Journal of
CHRONIC
DISEASES

VOLUME 14 . NUMBER 2

AUGUST, 1961

l. 14
961

Editorial

PYELONEPHRITIS, A PROBLEM IN PREVENTIVE MEDICINE

CALVIN M. KUNIN, M.D.
CHARLOTTESVILLE, VA.

From the Departments of Preventive Medicine and Medicine, University of Virginia School of Medicine

(Received for publication Jan. 5, 1961.)

MUCH attention currently is being focused upon the pathogenesis, epidemiology, diagnosis, and treatment of pyelonephritis. The pertinent literature has been summarized recently in editorials,[1,2] reviews,[3,4] and in an excellent symposium.[5] It is the purpose of this editorial to present arguments for considering this disease as largely preventable and to propose some of the means by which this end may be achieved.

Some of the advances which may make prevention of pyelonephritis possible are:

1. The recognition of the importance of pyelonephritis as the major cause of renal failure.[6,7]

2. The recognition of the relation of infections of the lower urinary tract to infection of the kidney and the significance of the ascending route of infection in pathogenesis.[7-10]

3. The introduction of the quantitative bacterial count, combined with the clean voided urine specimen, to provide the most sensitive indicator of urinary tract infections.[8,11]

4. The availability of antimicrobial therapy.[3]

5. The growing awareness on the part of physicians of the need to search diligently for structural or functional defects of the urethra, bladder, and ureters in patients with urinary tract infections.[12,13]

6. The delineation of the role of instrumentation of the urinary tract in producing infections and the means by which such trauma may be avoided or best managed to minimize infection.[8,14-19]

7. Progress in the field of urologic surgery on the significance of the megacystis syndrome,[20] the importance of reflux and bladder neck obstruction, as well as technical advances in reparative surgery.[21,22]

8. The epidemiologic approach to indicate the relative prevalence of subclinical infections in selected groups of patients and in the general population.[8,10,23-25]

9. The long-range longitudinal studies, now in progress, which will provide information relating the importance of subclinical infections to irreversible damage of the kidneys, hypertension, and complications of pregnancy.[10,25,26]

Urinary tract infections in females are very common, occurring in about 15 to 30 per cent of hospital patients,[8,23,24] 6 to 8 per cent of pregnant women,[10] 6 per cent of female patients in an outpatient department,[8] and at least 1 per cent of healthy school girls.[25] Infections in males are most common in the neonatal period, at which time they are usually associated with congenital anomalies, and in the age group over 50, when prostatism becomes an important factor. Most infections in males between these age extremes are related to instrumentation of some type.[24] In view of these data and the advances listed, one may question two common medical practices which, although at extreme poles from each other, seem on the one hand to represent complacency and on the other tilting at windmills. The former practice is the unwarranted[27-29] offhand dismissal of urinary tract infections with the statement, "you have just a touch of pyelitis, there is no need for concern"; the latter is exemplified by the sometimes fantastic extremes to which clinicians may go in "restoring electrolyte balance" and in the use of antibiotics in patients with irreversible renal damage. Of particular concern is the tremendous effort in medical education and research on the physiology and treatment of uremia. Would we not better serve our patients by directing these talents and resources to the *prevention* of renal failure?

The following measures are suggested as preliminary steps in preventing pyelonephritis and its consequences:

1. Pursuit of studies already mentioned on the long-term significance of asymptomatic bacteriuria.

2. The use of the quantitative bacterial count of the clean voided urine specimen to detect early infections in school girls, adult women, and particularly pregnant women. This may be accomplished on a mass basis in schools (as in Waynesboro, Virginia[25]), in the physician's office practice, or by the establishment in hospitals and health departments of clinics for the detection of urinary tract infection. Industrial plants, particularly those with large numbers of female employees, would be particularly suitable for such programs.

3. Aseptic care of indwelling catheters, used only with discretion, combined with tidal drainage or similar intermittent wash procedures incorporating bactericidal solutions such as acetic acid.[30] This calls for training of personnel in the use of drainage apparatus and strict attention to detail.

4. Early and vigorous therapy of urinary tract infection aimed at eradication not only of symptoms and pyuria, but of bacteria as well. This may, in many instances, require long-term antimicrobial therapy.

5. Complete urologic evaluation of patients with urinary tract infections to permit treatment of structural and functional abnormalities.

6. Continued research on the mode of entry of bacteria into the urogenital tract (particularly of the female), and the host mechanisms by which such organisms are cleared.

Extensive epidemiologic studies investigating the relation of pyelonephritis to hypertension, perinatal mortality, and prematurity are being conducted by Kass and his group.[31] Switzer,[32] working in Japan, has presented evidence to support the view, ". . . that if pyelonephritis causes hypertension, this is a rare event."

We are currently investigating the epidemiology of urinary tract infections in 12,000 school children in Charlottesville and Albemarle County, Virginia. We hope to learn: (1) the relative prevalence of overt and covert cases, (2) the exact age and sex distribution, (3) whether or not there are familial, social, or racial factors which influence this prevalence, (4) the reinfection rate in children given a short course of chemotherapy, (5) factors which may be of importance in producing reinfection, and (6) the yield from multiple studies of the same population. Our experience indicates that such a program, clearly presented to a community, can be accepted overwhelmingly and without reservation. Currently, voluntary participation in this area is 95 per cent of the maximum, and includes public, private, rural, and urban schools.

It seems to us that we now can begin to bring our vast medical resources to bear on this problem and develop a major attack on the prevention of pyelonephritis with the same vigor we have exerted in the past on diseases such as tuberculosis and poliomyelitis.

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PREVENTION OF DEGENERATIVE DISEASE: A CONTROLLED STUDY OF ANTICOAGULANT PROPHYLAXIS

J. R. WHITTIER, M.D.,*
C. KORENYI, M.D.,**
D. F. KLEIN, M.D.,***
AND W. FOLEY, M.D.****
JAMAICA, N. Y.

From Creedmore State Hospital, Jamaica, N. Y.
(Received for publication Nov. 30, 1960)

TISSUE damage accompanying atherosclerosis results from: (1) atherogenesis, (2) thrombosis, or (3) thromboembolism. Anticoagulant medication has been recommended for prophylaxis of thrombosis and thromboembolism since 1945.[1] The few controlled studies of the effect of long-term anticoagulant medication on mortality or morbidity due to vascular disease have employed populations selected for antecedent thrombotic or thromboembolic morbidity.[2,3,4]

A controlled prophylactic trial of anticoagulant medication in an aged hospitalized population with a high mortality rate should give some indication of the extent to which thrombotic and embolic processes contribute to mortality. Information respecting the influence of such medication on the morbidity rate might also be expected.

It was considered appropriate to conduct such a prophylactic trial in a large state hospital because data have been published repeatedly demonstrating that for psychotic individuals aged 60 and over, 1 in 5 would be dead 30 days after admission to a state hospital, and 1 in 2 would be dead within a year.[5] With few exceptions, the clinical diagnosis for these patients is "chronic brain syndrome associated with senile brain disease, with psychotic reaction" (009–79x.xl) ("psychosis with senility"—PS) or "chronic brain syndrome associated with cerebral arteriosclerosis, with psychotic reaction" (009–516.xl) ("psychosis with cerebral arteriosclerosis"—PCAS). The latter diagnosis is made one-third more frequently than the former.[6] Finally, the usual cause of death recorded for these patients is "arteriosclerotic heart disease." The processes of atherosclerotic vascular degeneration may therefore be presumed to be active and rapid in such a population.

Support for this study was received from the following: Lasker Foundation (grant-in-aid), Abbott Laboratories (medication provision in part), Public Health Service, Grant M-3501 (A) National Institute of Mental Health.

*Director of Psychiatric Research, Creedmoor Institute for Psychobiologic Studies, Jamaica 27, N. Y.

**Senior Research Psychiatrist, Creedmoor Institute for Psychobiologic Studies, Jamaica 27, N. Y.

***Research Associate, Department of Experimental Psychiatry, Hillside Hospital, 75-59 263rd Street, Glen Oaks, N. Y.

****Associate Professor of Clinical Medicine, Cornell University Medical College, 1300 York Avenue, New York 13, N. Y.

The study reported here, organized in 1957, went into execution in October of that year.

MATERIAL

Patients were selected continuously from weekly Records Office lists to include all males aged 60 and over, admitted for the first time to a state hospital, with no history of bleeding ulcer in the gastrointestinal tract or presence of ulcer in this tract, no hematuria or blood dyscrasia, blood pressure below 200 systolic, 120 diastolic, ambulatory status, reasonable bowel and urinary continence, and cooperative to oral medication and procedures.

Selection was made regardless of recognized pre-existing vascular morbidity because of the high incidence of atherosclerotic changes in human pathologic material over 60 years of age[7] and our present inability precisely to discriminate patients with such disease from those not having it, or between either of these groups and patients with combined vascular and neuronal degeneration in a state hospital population.

By 3 screening studies (Table I), 162 patients were accepted who met criteria from a sample of 540. (Observations during the screening studies were also termed "initial.") These 162 patients were distributed in one of three groups: (1) treated, T; (2) control, C; or (3) observation, O, by a continuous random serial triplet method, so that each group had 54 patients at the time of this report.

METHOD

Administration of Medication, Anticoagulant Laboratory Control, and Observational Methods.—Patient screening and group distribution processes were completed and medication begun within one month of admission. The desired prothrombin time range for patients on anticoagulant was set at between 20 and 30 seconds, with a control of 13 to 15 seconds by the Quick method. Dicumarol* was used exclusively, since experience with it is most extensive and it was not the purpose of the study to compare different anticoagulants. In the treated group, the average weekly dose of Dicumarol was 355 mg., ranging from 145 to 760 mg. The average number of prothrombin time determinations per week was 2.8. Daily graphic records of dosage and prothrombin time were found invaluable in maintaining control.

Prothrombin time was above 20 seconds for an average of 90 per cent (range 70 to 100 per cent) of the total days on which patients received anticoagulant medication, so that a relatively "ideal" therapeutic level was maintained.

The treated group received anticoagulant medication and periodic observations (see Table I). The control group received a placebo, and the same periodic studies without exception. The observation group received no medication, and was not subject to periodic study, other than observation for mortality. The purpose of the observation group was to control for "trial process" effects, including the acts of medicating and observing. Patients were added cumulatively to

*Abbott Laboratories.

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TABLE I. SCREENING PROCESS

SCREEN	PROCEDURES
1	History and administrative status
2	Physical, neurological, and mental examinations
3	Laboratory and special tests (including Rumpel-Leede sign*; ECG*; chest x-ray; complete blood count; routine urinalysis; fasting blood sugar and blood nonprotein nitrogen* determinations; sedimentation rate; hematocrit*; blood type and Rh determination; bleeding, clotting, prothrombin* and serum prothrombin, and clot retraction times; and stool for guaiac positivity)

*Periodic observations. White cell count and microscopic urinalysis was also periodic.

all three groups, and the study population at any time was the algebraic sum of admitted patients meeting the criteria, less screening rejects and those dropped out by death, discharge, or discontinuation. Since research staff nurses saw each patient in treated and control groups daily, continuous close observation was insured. Morbidity incidents were given immediate diagnostic action, and recommendations were made to Supervising Psychiatrists respecting disorders not due to anticoagulant medication. Special efforts were made to obtain consent for autopsy when a patient died.

Controls for Blindness of Study.—The hospital staff responsible for medical-psychiatric management (distinct from the research staff responsible for anticoagulant management) knew that a patient was in the study and might be receiving anticoagulant medication. Patients remained on assigned wards, without segregation. Every effort was made by research staff nurses and physicians to handle treated and control patients in an identical manner.

The few patients discharged from the hospital were considered beyond the control required, and were dropped from the study.

Analytic and Statistical Methods.—Relevant information abstracted from hospital records, together with research data, was transferred to needle-sort cards (McBee) for analysis. The "sign test for two related samples" was applied to test the hypothesis concerning true differences in mortality between "treated" and "control" samples.[8]

This report describes findings for the 27 month period ending Dec. 31, 1959.

RESULTS

Population Characteristics.—The majority of the patients were covered by the two diagnoses, "chronic brain syndrome associated with arteriosclerosis, with psychotic reaction" and "chronic brain syndrome associated with senile brain disease, with psychotic reaction" (Table II), and fell into the age decade 70-79 years (Table III). The equivalence of distribution between the two groups in these tables shows that the random selection was effective. Table IV presents "indication" for anticoagulant therapy by group distribution of such cases. Such therapy was "indicated" for approximately one-third of the patients in T and O groups on the basis of history of cerebral or coronary thrombosis (16 patients each in T and O groups), and approximately one-fifth of the patients

TABLE II. DIAGNOSIS DISTRIBUTION FOR ACCEPTED PATIENTS

	T GROUP	C GROUP	O GROUP
Chronic brain syndrome: cerebral arteriosclerosis with psychotic reaction	20	19	16
Chronic brain syndrome: senile brain disease with psychotic reaction	17	17	15
Involutional psychotic reaction	7	9	8
Chronic brain syndrome: alcohol intoxication with psychotic reaction	2	1	7
Affective reaction	1		1
Schizophrenic reaction	2		1
Other	5	8	6
Total	54	54	54

TABLE III. AGE DISTRIBUTION FOR ACCEPTED PATIENTS

DECADE	T GROUP	C GROUP	O GROUP
60–69	20	18	27
70–79	25	28	23
80–89	7	7	3
90–99	2	1	1
Total	54	54	54

TABLE IV. INDICATION FOR ANTICOAGULANT THERAPY AS PROPHYLAXIS VERSUS GROUP DISTRIBUTION (54 PATIENTS IN EACH GROUP)

	T GROUP		C GROUP		O GROUP	
	NO.	%	NO.	%	NO.	%
History of cerebral thrombosis	11	20	7	13	9	17
Residue of cerebral thrombosis	3	6	5	9	5	9
History of coronary thrombosis	5	9	3	6	7	13
ECG evidence of coronary arteriosclerosis	28	52	25	46	20	37

in C group. However, on the basis of residual clinical findings, the percentage was much higher, namely, 58 per cent in T group, 55 per cent in C group, and 46 per cent in O group.

Outcome.—In terms of mortality, the pertinent figures were 6, 15, and 14 for T, C, and O groups, representing rates of 11, 28, and 26 per cent, respectively. The sign test for two related samples was applied in statistical analysis of the difference in mortality between T and C groups (Table V). The "null hypothesis" was rejected at the 5 per cent level of confidence, indicating that the difference was probably due to the prophylactic anticoagulant medication and not to chance. The difference between T and O groups was significant at the 5.8 per cent prob-

ability level. By nature of the design, the T and C groups were more comparable with regard to the study operations of medicating and observing than were the T and O or C and O groups. There was equivalence for the three groups regarding discharges. A trend to slightly greater incidence of morbidity for the T group will be commented upon later.

Total patient days in the T and C groups were 9,818 and 6,810, respectively, with respective means of 182 and 126 patient days, to date of report. The higher figures for the T group are a reflection of the lower mortality rate.

Autopsy success was 33 per cent for the 6 patients in the T group who died, 53 per cent for the 15 patients in the C group who died, and 14 per cent for the 14 patients in O group (Table VI, together with mortality figures). There was a statistically significant difference between the T and C groups in survival time of patients who died, although survival times of the patients in the T and O groups who died were not different; differences in comparability between T and C and between T and O groups were noted previously with respect to mortality.

There was a slightly greater incidence of morbidity for the T group, 26 compared to 19, primarily from pneumonia and cellulitis (Table VII). This difference is interpreted as a possible consequence of the "early detection function" of prothrombin time determinations. By this is meant that when a patient under prophylactic anticoagulant medication develops an infection, his prothrombin time will rise, so that these cases came earlier and more certainly to clinical recognition. The single instance of coronary thrombosis appears in the control group; one instance of congestive heart failure appears in the treated group. Table VII shows only morbidity not resulting in death.

The primary cause of death for patients in T, C, and O groups is shown in Table VIII. The cause was determined by the medical consultant, after review of all clinical records and of autopsy reports where available. The first three causes in the table represent consequences of vascular degenerative disease.

The primary cause of death due to vascular disease is shown again in Table IX, arranged by trial group, and by mental diagnosis.

TABLE V. MORTALITY, MORBIDITY, AND DISCHARGES BY GROUPS (54 PATIENTS IN EACH GROUP)

	T GROUP	C GROUP	O GROUP
Mortality	6	15	14
Morbidity*	26	19	
Discharged	14	14	16

*Includes all types, except those resulting in death; it was not possible to observe morbidity in the observation (O) group.

TABLE VI. MORTALITY, AUTOPSY, AND SURVIVAL TIME BY GROUPS (54 PATIENTS IN EACH GROUP)

	T GROUP	C GROUP	O GROUP
Mortality	6	15	14
Autopsy cases	2	8	2
Survival time* (mean days)	166	66	163

*Patients who died only.

TABLE VII. MORBIDITY BY GROUPS

	T GROUP	C GROUP
Anemia	1	
Bell's palsy		1
Icterus		1
Arthritis	1	1
Viral infection		1
Coronary thrombosis		1
Pneumonia	6	2
Cellulitis	5	2
Senile dermatitis with secondary infection	4	4
Enteritis	1	1
Fracture		1
Scalp laceration with secondary infection	1	1
Upper respiratory infection	2	3
Infected great toe	1	
Drug allergy	2	
Congestive heart failure	1	
Carcinoma of rectum	1	
Total episodes	26	19

TABLE VIII. PRIMARY CAUSE OF DEATH BY GROUPS

	T GROUP	C GROUP	O GROUP
1. Cerebral thrombosis	1	2	
2. Coronary thrombosis	1 (1)	1	1
3. Arteriosclerotic heart disease	1	4 (2)	9 (1)
4. Subdural hematoma	1 (1)	1 (1)	
5. Pneumonia	1	5 (4)	3
6. Septicemia	1		1 (1)
7. Strangulated hernia		1 (1)	
8. Carcinoma of lung		1	
Total	6	15	14

Numbers in parentheses indicate number of cases confirmed by autopsy.

TABLE IX. PRIMARY CAUSE OF DEATH DUE TO VASCULAR DISEASE, BY TRIAL GROUP, AND BY MENTAL DIAGNOSIS

	T GROUP	C GROUP	O GROUP
1. Cerebral thrombosis	1–PS*	1–PS 1–PCAS†	
2. Coronary thrombosis	1–PS	1–PS	1–PS
3. Arteriosclerotic heart disease	1–PS	2–PS 2–PCAS	3–PS 5–PCAS 1–IM‡
Total	3	7	10

*PS, psychosis with senility.
†PCAS, psychosis with cerebral arteriosclerosis.
‡IM, involutional melancolasia.

The distribution of diagnoses of discharged patients (Table X) indicates no difference in discharge rate for the three groups. Patients with the psychiatric diagnosis "involutional psychotic reaction" tend to have greater probability of discharge than patients with other diagnoses.

There were 11 episodes of major hemorrhage in the treated group of 54 patients and no episodes in the control group of the same number. Cases of hemorrhage without other causes competent to produce hemorrhage, and believed under the circumstances to be caused by anticoagulant medication, were classified as "due to anticoagulant." There were 6 such cases in the treated group. In 5 of these, the hemorrhages were from the alimentary tract. In one, there occurred a marked dermal ecchymosis with negative Rumpel-Leede sign.

Cases where the bleeding arose from a known hemorrhagic site but in which the bleeding appeared aggravated by, precipitated by, or prolonged by anticoagulant medication were classified as "aggravated by anticoagulant." There were 5 such patients, with hemorrhagic sites demonstrated as follows: 3 patients with lesions in the alimentary tract (esophageal varices, duodenal ulcer, and adenocarcinoma of colon); 1 patient with marked dermal ecchymosis with positive Rumpel-Leede sign and subsequent anemia; 1 patient with traumatic subdural hematoma.

TABLE X. DIAGNOSIS DISTRIBUTION OF DISCHARGED PATIENTS

	T GROUP	C GROUP	O GROUP
Chronic brain syndrome: cerebral arteriosclerosis with psychotic reaction (PCAS)	4	3	2
Chronic brain syndrome: senile brain disease with psychotic reaction (PS)	2	1	2
Involutional psychotic reaction (IM)	4	6	6
Chronic brain syndrome: alcohol intoxication with psychotic reaction			3
Affective reaction	1		1
Schizophrenic reaction	1		
Psychotic depressive reaction	2	2	1
Chronic brain syndrome: central nervous system syphilis with psychotic reaction			1
Other		2	
Total	14	14	16

For the 6 cases "due to anticoagulant medication" the rate of hemorrhagic episodes was 0.61 per thousand days of medication. For the 5 cases in which the bleeding was "aggravated by anticoagulant medication," the rate was 0.51 per thousand days of medication. Wright, Marple, and Beck[9] observed rates of 1.8 and 1.2 per thousand for episodes "due to" and "aggravated by" anticoagulant medication, respectively, in patients treated for myocardial infarction. Closer hematologic control possible with an intramural population probably is the explanation for the considerably lower rates attained in the study reported here.

Minor hemorrhagic episodes showed a rate of 3.2 per thousand days of therapy for the treated group, manifesting as ecchymosis, hematuria, and epistaxis, and 0.44 for the control group, manifesting as ecchymosis and epistaxis.

Miscellaneous Observations.—

Previously unrecognized medical disorders: As a result of the screening procedures, 11 major and previously unrecognized medical disorders were revealed in 540 patients: marked anemia 3, chronic lymphocytic leukemia 2, polycythemia vera 1, myocardial infarction 2, abdominal aneurysm 1, hypertension 1, peripheral neuropathy 1.

Hematocrit: Closed charts of 36 patients in the treated group without hemorrhage, having initial and final hematocrits, were available for analysis. Initial mean hematocrit was 43.14 per cent and final mean hematocrit was 39.14 per cent. These figures were compared with those from closed charts of 39 similar patients in the control group, where the initial mean hematocrit was 42.24 per cent and final mean hematocrit was 41.05 per cent. The difference between treated and control groups on the basis of the decrease observed within each group (4 and 1.19 per cent, respectively) was statistically significant at the 5 per cent level of confidence. The mean duration of therapy for the treated and control groups was 195 days and 117 days, respectively. Either some degree of anemia accompanied Dicumarol administration in this study, or a period of observation longer by 2 months for the treated group brought about the difference. The phenomenon could not be checked by hemoglobin or erythrocyte counts, which were not periodic. Chronic hemorrhage was detected by slow progressive decrease in hematocrit in several cases.

Patients dropped from study: The mortality rate for patients dropped (other than those discontinued for hemorrhagic complication) was 42 per cent in the treated and 36 per cent in the control group. Discontinuation was for intercurrent medical disorder unrelated to anticoagulant medication (8 in Group T, 4 in Group C) or miscellaneous other causes (4 in Group T, 7 in Group C).

Discharged patients: Table XI shows the over-all discharge number in each group. The combined mean of control and observation groups shows that the rates of discharge were approximately the same for patients who were on anticoagulant and those who were not (50 per cent compared to 53.5 per cent discharged outright, and 50 per cent compared to 41.5 per cent to convalescent care).

TABLE XI. FOLLOW-UP OF DISCHARGED PATIENTS

GROUP	TOTAL	OUTRIGHT	CONVALESCENT CARE	TRANSFERRED TO OTHER HOSPITAL	NURSING HOME
T	14	7	7		
C	14	10	3		1
O	16	6	8	1	1

Follow-up study of 11 treated patients with a pretrial history of cerebral thrombosis showed 2 (18 per cent) in study, 2 (18 per cent) dropped, 4 (36 per cent) discharged, and 3 (27 per cent) died. For 7 control patients with such a history, the figures were 3 (43 per cent) in the study, 1 (14 per cent) dropped, 1 (14 per cent) discharged, and 2 (28 per cent) died.

Follow-up study of 5 treated patients with a history of coronary thrombosis showed 2 (40 per cent) in the study, 2 (40 per cent) dropped, and 1 (20 per cent) discharged. For 3 control patients with such a history, the figures were 1 (33 per cent) in the study, 1 (33 per cent) dropped, and 1 (33 per cent) discharged. The figures are too small for meaningful statistical treatment.

DISCUSSION

There are two points to be made in discussion. First, it is important to recognize that this study evaluates the prophylactic effects of Dicumarol anticoagulant in a population selected by the criterion of admission to a state hospital at age 60 or over, such a population being characterized by a high mortality rate due to a variety of factors. Among these the processes of thrombosis and embolism were hypothesized to be heavily contributory. The administration of Dicumarol anticoagulant was intended to prevent these processes in any part of the atherosclerotic vascular tree.

The study is therefore not easily comparable to the multi-institutional or cooperative studies recently reported from the Veterans Administration and Public Health Service.

Second, results of the study are considered definitive respecting mortality. Practical application of prophylactic anticoagulant medication will wait upon development of medications not requiring the unremitting vigilance against hemorrhage which Dicumarol demands, and upon better differentiation of individuals at risk from atherosclerotic degenerative disease from those without such risk.

SUMMARY

A placebo-controlled trial of the prophylactic value of anticoagulant (Dicumarol) medication was conducted on a population of 162 subjects selected from 540 male patients aged 60 and over admitted to a state hospital for the first time, distributed in random manner into treated, control, and observation groups. For the population selected, under rigorous clinical control, it was observed that:

1. Mortality in patients receiving Dicumarol was 11 per cent compared with 28 per cent in patients receiving placebo. This difference was statistically significant at the 5 per cent level of confidence.

2. Mean survival time for patients in the study who died was more than twice as long for patients receiving Dicumarol.

3. Major hemorrhage occurred in 20 per cent of patients receiving Dicumarol. In 9 per cent the hemorrhage was from a site in which the bleeding appeared "aggravated by anticoagulant medication." In 11 per cent the hemorrhage was without other causes competent to produce hemorrhage and was believed "due to anticoagulant medication."

We would like to credit the following for their assistance in the study: from the Institute, G. G. Haydu, M.D., A. D. Dhrymiotis, M.D., and A. B. Crum, M.D.; biochemist L. Goldschmidt, Ph.D., and staff; social worker J. R. Crawford, M.A.; the nursing and stenographic staffs under E. Alesi, R.N., and M. Seaman, respectively. From the hospital, the Director, H. D. LaBurt, M.D., O. K. Diamond, M.D., G. Savitscus, M.D., and W. Brinitzer, M.D., provided cooperation. Consultants included H. Brill, M.D., I. S. Wright, M.D., and E. McDevitt, M.D.

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RECENT TRENDS IN MORTALITY FROM CEREBROVASCULAR ACCIDENTS IN THE UNITED STATES

CHARLES M. WYLIE, M.D., DR.P.H.*
BALTIMORE, MD.

From the School of Hygiene and Public Health, The Johns Hopkins University

(Received for publication Dec. 15, 1960)

IN MOST of the advanced countries, vascular lesions of the central nervous system are the third most numerous cause of death, outranked only by diseases of the heart and malignant neoplasms. In the United States, however, central nervous system vascular lesions have not attracted their proportional share of interest and research funds, as have heart disease and cancer. No voluntary agency has adopted cerebrovascular accidents as its primary health problem. Few flickers of public interest occur when V.I.P.'s die from "cerebral hemorrhage."

With some notable exceptions, apathy prevails also among physicians. Perhaps we have felt inadequate in dealing with hemiplegia, which demands of the physician "a presence radiating assurance and encouragement for the patients and those around them." Perhaps we believe that cerebrovascular accidents attack old people only, that the prognosis is invariably poor, that they affect brains already addled and senile with atherosclerosis.

All these beliefs are partly true. Of 190,758 deaths from cerebrovascular accidents in 1958 in the United States, more than half were of persons 75 years of age and older.[1] Of those admitted to hospitals in recent years, about 20 per cent die in the initial phase, and almost 60 per cent die within 4 years.[2] However, CNS vascular lesions affected large numbers of younger persons as well—16,050 of the deaths in 1958 were in the age group under 55.[1] One is not justified, therefore, in viewing cerebrovascular disease as merely Nature's method for disposing of the elderly.

The relative neglect of CNS vascular lesions is found also in the field of epidemiology, where studies are much needed to supplement clinical knowledge of these conditions. The purpose of this paper is to reduce this epidemiologic gap by analyzing mortality statistics for such lesions, particularly in relation to age, sex, and race in the population of the United States.

HISTORY OF CARDIOVASCULAR DIAGNOSIS

The diagnosis of cerebrovascular accidents is historically more ancient than that of heart disease. "Apoplexy" was a recognized clinical syndrome and

This study was assisted by a grant from the National Institutes of Health.
*Assistant Professor, Public Health Administration.

cause of death before the time of Hippocrates.[3] Morgagni studied cerebrovascular accidents extensively in the mid-eighteenth century. Many additional studies, such as those of Gintrac (1869), Hammond (1881), and Dana (1895) were published in the second half of the nineteenth century.

By the beginning of the twentieth century, cerebral hemorrhage, thrombosis, and embolism were recognized diagnoses, still infrequent but beginning to replace the vaguer terms of "stroke," "apoplexy," and "hemiplegia." However, subarachnoid hemorrhage, first diagnosed in a living patient in 1875,[3] was a rare diagnosis until the 1920's. In the last decade, thrombosis of the internal carotid and vertebral arteries, resulting in hemiplegia, has been frequently described in medical literature, although this diagnosis is still numerically unimportant.

In contrast, the diagnosis of diseases of the heart has developed more recently.[4,5] The relationship of angina pectoris to coronary disease became widely known in the early nineteenth century, as did valvular disorders of the heart. Rheumatic heart disease was well established and hypertensive disease was beginning to be recognized about 1900. It was not until 1921 in the United States that White and Myers presented an etiological classification of cardiac disease close to that now used in classifying causes of death.

Also in the 1920's, coronary occlusion and myocardial infarction were being more frequently diagnosed by general physicians, and the diagnostic help of the electrocardiograph was increasingly used. No comparable aid has emerged to encourage early diagnosis of cerebrovascular disease.

These recent developments in diagnosing cardiac disease have changed considerably the diagnostic habits of physicians, particularly when faced with cases of sudden death. A large proportion of such deaths, which at the turn of this century might have been attributed to the well-recognized "apoplexy," may now be certified as the more fashionable "coronary occlusion." Moreover, coding procedures have also affected mortality statistics; many deaths, formerly coded as CNS vascular lesions, are now classified in other cardiovascular categories. For example, the cause of death in cases in which two or more causes were listed was assigned on an arbitrary basis before 1948; since then, the certifying physician has assigned the primary cause. Fortunately, the National Office of Vital Statistics has computed figures for 1939 through 1948 which compensate for the coding change and which are comparable with those after 1948.[6]

The change in medical concepts makes it unfeasible to compare death rates from cerebrovascular disease in the first decades of this century with death rates in more recent years. As changes in diagnostic ideas have been less drastic since 1939, however, this paper describes trends from that time to 1959.

RECENT TRENDS IN MORTALITY (TABLE I)

Crude death rates from CNS vascular lesions have increased by about 9 per cent since 1939. Average mortality during 1939-1940 was 101.3 per 100,000 population, while the average during 1957-1958 was 110.2. In the first decade of the same period, however, crude death rates from other diseases of the cardio-

vascular system increased more rapidly. Thus, in 1939-1940, cerebrovascular accidents caused 22.9 per cent of all deaths from cardiovascular disease; by 1949-1950, this had fallen to 20.9 per cent; since 1951, there has been no change in this percentage. In contrast, cerebrovascular accidents have caused a slowly increasing proportion of all deaths occurring in the population; the proportion has risen from 9.5 per cent in 1939-1940, to an average of 11.6 per cent in 1957-1958.

TABLE I. TRENDS BETWEEN 1939 AND 1958 IN ANNUAL DEATH RATES PER 100,000 POPULATION FROM CNS VASCULAR LESIONS (330-334)*

	1939-1940	1941-1942	1943-1944	1945-1946	1947-1948	1949-1950	1951-1952	1953-1954	1955-1956	1957-1958
Average crude death rate	101.3	101.6	106.8	106.1	102.7	102.5	106.7	105.7	106.2	110.2
Per cent of all cardiovascular diseases	22.9	22.4	21.9	21.9	21.0	20.9	21.4	21.4	21.4	21.4
Per cent of deaths from all causes	9.5	9.7	10.0	10.3	10.3	10.6	11.1	11.3	11.4	11.6

Source: Vital Statistics of the United States, 1950-1958.[7]

*Expressed as average crude death rate, as percentage of all diseases of the cardiovascular system (330-334, 400-468), and as percentage of deaths from all causes.

The greater proportion of older persons in the population and increasing death rates in older age groups have caused the rise in crude death rates. In younger age groups, death rates from CNS vascular lesions have fallen. To study the same age, sex, and racial groups at different times, Table II gives the example of white males aged 55 to 64. Their average annual death rate during 1949-1951 was 183 per 100,000; by 1956-1958 this figure had fallen to 153. Table II shows also that this decrease of 16.1 per cent is significantly greater than the 0.7 per cent fall in death rates from other cardiovascular diseases and the 3.4 per cent fall in deaths from all causes.

The change in mortality has not been equal in all age, sex, and race groups (Table III). In general, younger persons show the greater decrease. For example, between 1950 and 1957, average rates for men in the age groups 45-54 and 55-64 fell by 18 and 16 per cent, respectively; for men 65-74, the fall was 3 per cent; for men 75-84, the rates actually increased by 5 per cent.

Death rates for women decreased more than for men of the same age and race (Table III). Death rates for white women, for example, fell nearly twice as much as for white men. When we contrast the change in rates for whites and non-whites, we find that white death rates usually fell more than non-white rates. Moreover, rates have risen for whites in the age group 75 to 84; in both non-white men and women 65 to 74 years of age, mortality from CNS vascular lesions rose by more than 30 per cent between 1950 and 1957.

MORTALITY BY AGE (TABLE IV)

Death rates from vascular lesions of the central nervous system rise with age. Table IV shows that, after a small peak in infants under 1 year, the death rate

TABLE II. DEATH RATES IN THE UNITED STATES FROM CNS VASCULAR LESIONS (330–334), FROM OTHER CARDIOVASCULAR DISEASES (400–468), AND FROM ALL CAUSES, FOR WHITE MALES 55 TO 64 YEARS OF AGE

YEAR	DEATH RATES PER 100,000		
	CNS VASCULAR LESIONS	OTHER CARDIOVASCULAR DISEASES	ALL CAUSES
1949–1951 average	182.5	1124.7	2313.8
1956–1958 average	153.2	1117.4	2234.4
Per cent change	−16.1	−0.7	−3.4

Source: Vital Statistics of the United States, 1950-1958.[7]

TABLE III. TRENDS BETWEEN 1949 AND 1957 IN DEATH RATES (PER 100,000 PERSONS) FROM CNS VASCULAR LESIONS IN U.S. POPULATION BY AGE, SEX, AND RACE

YEAR	MALES (AGE IN YEARS)				FEMALES (AGE IN YEARS)			
	45–54	55–64	65–74	75–84	45–54	55–64	65–74	75–84
Whites								
1949–1951 average	53.8	182.5	569.4	1548.4	55.6	156.5	495.4	1471.4
1953	51.2	176.9	559.6	1592.2	51.0	143.4	476.5	1511.1
1956–1958 average	43.9	153.2	551.6	1620.7	37.2	115.3	441.6	1486.6
Per cent change	−18.4	−16.1	−3.1	+4.7	−33.1	−26.3	−10.9	+1.0
Non-Whites								
1949–1951 average	203.2	498.2	779.7	1327.0	242.1	556.2	769.6	1344.5
1953	203.7	468.7	917.0	1361.8	227.8	478.0	900.3	1378.8
1956–1958 average	163.3	453.0	1065.9	1419.7	183.2	458.3	1021.1	1309.1
Per cent change	−19.6	−9.1	+36.7	+7.0	−24.3	−17.6	+32.6	−2.6

Source: Vital Statistics of the United States, 1950-1958.[7]

remains low between 1 and 24 years. About this age, death rates climb continuously to a maximum in those 85 and older. This mortality pattern occurs in both sexes, and in the white and non-white population in the United States.

As age rises from 0 to 44 years, deaths from CNS vascular lesions form a decreasing proportion of all cardiovascular deaths; in contrast, from 55 years upward, such lesions form a steadily increasing proportion. Moreover, CNS vascular lesions cause an increasing percentage of all deaths as age increases. In non-white females, for example, CNS vascular lesions cause 0.1 per cent of all deaths under one year of age, 11.5 per cent of all deaths between 35 and 44,

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TABLE IV. 1958 DEATH RATES FROM CNS VASCULAR LESIONS, BY AGE, SEX, AND RACE (PER 100,000 ESTIMATED MID-YEAR POPULATION)

RACE	SEX	TOTAL	AGE IN YEARS										
			UNDER 1	1–4	5–14	15–24	25–34	35–44	45–54	55–64	65–74	75–84	85+
White	Male	104.8	4.9	1.1	0.7	1.8	3.7	11.4	42.4	149.0	552.6	1637.9	3639.2
	Female	112.0	3.7	0.7	0.6	1.3	3.6	10.8	35.5	111.6	434.9	1494.0	4206.8
Non-white	Male	121.8	8.7	2.3	1.1	2.8	13.0	48.7	157.9	459.4	1131.2	1492.0	1876.3
	Female	124.8	8.4	1.3	1.0	3.0	16.8	62.9	171.7	443.8	1060.5	1375.6	1847.9
Total		100.1	4.9	1.0	0.7	1.7	4.9	15.6	51.1	156.5	529.3	1547.8	3751.0

Source: Vital Statistics of the United States, 1958.[1]

and 20 per cent of all deaths at 65 and above. A similar progressive rise occurs in all races and both sexes.

SEX DIFFERENCES IN MORTALITY (TABLE IV)

In both races, women have the higher crude death rates (Table IV). In whites, the higher rate for women is related to the different age distribution of the two sexes, since white men have higher deaths rates from CNS vascular lesions than white women of the same age. Only at age 85 and above do women have the higher rate. In non-whites between the ages of 15 and 54, women have slightly higher rates; while below 15 and above 54 years of age, rates for males are higher.

CNS vascular lesions cause a greater proportion of all deaths from cardiovascular disease in women than in men, both white and non-white. The sex difference in these proportions is more marked between the ages of 35 and 64 than at younger and older ages, and more marked in whites than in non-whites. For example, at ages 45 to 54, cerebrovascular accidents caused 10 per cent of all cardiovascular deaths in white males and 25 per cent in white females; 22 per cent in non-white males and 29 per cent in non-white females.

Similarly, CNS vascular lesions cause a greater percentage of all deaths in women than in men at all ages. Over 65 years, for instance, 16 per cent of deaths of non-white males and 20 per cent of all deaths of non-white females result from CNS vascular lesions.

RACIAL DIFFERENCES (TABLE IV)

Death rates from CNS vascular lesions are higher in non-whites than in whites of the same age and sex under 75 years of age (Table IV). Over that age, rates in non-whites are lower. Between the ages of 25 and 64, the rates in non-whites are three to five times those of whites. Above and below this range, the race difference is much smaller.

In general, whites die from CNS vascular lesions at older ages than do non-whites. The median age at death from such lesions in 1958 was 74 and 77 for white men and women, respectively, and 64 and 65 for non-white men and women.

CNS vascular lesions form a consistently higher percentage of all deaths from cardiovascular disease in non-whites, at all ages and for both sexes. Similarly, they cause a higher proportion of all deaths in non-whites than in whites.

RECENT TRENDS IN DIFFERENTIAL DIAGNOSES (TABLE V)

Since 1949, deaths from CNS vascular lesions have been coded in four diagnostic groups; subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism and thrombosis, and other and ill-defined lesions. Table V shows that death rates from subarachnoid hemorrhage and from cerebral embolism and thrombosis have increased greatly in the last decade; death rates from cerebral hemorrhage have decreased slightly, and from "other and ill-defined lesions" have fallen considerably.

TABLE V. TRENDS BETWEEN 1949 AND 1958 IN ANNUAL DEATH RATES PER 100,000 POPULATION FROM CNS VASCULAR LESIONS (330–334) AND FROM THE COMPONENT DIAGNOSTIC GROUPS

	1949–1950	1951–1952	1953–1954	1955–1956	1957–1958	PER CENT CHANGE
All CNS vascular lesions (330–334)	102.5	106.7	105.7	106.2	110.2	+7.5
Subarachnoid hemorrhage (330)	2.0	2.6	2.9	3.2	3.5	+75.0
Cerebral hemorrhage (331)	69.6	71.2	68.7	66.8	66.5	−4.4
Cerebral embolism and thrombosis (332)	16.2	19.4	22.5	25.6	30.0	+85.2
Other and ill-defined lesions (334)	14.7	13.5	11.6	10.6	10.2	−30.6

Source: Vital Statistics of the United States. 1950-1958.[7]

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Most likely these trends reflect changes in diagnostic habits of physicians. In recent years, medical papers have stressed the need for more precise diagnosis, particularly of subarachnoid hemorrhage where surgical treatment is possible. The increased efforts to reach a precise diagnosis has reduced the numbers of "ill-defined" diagnoses.

DISCUSSION OF THE FINDINGS

The changing diagnostic habits and coding procedures discussed earlier in this paper partly account for the decreasing age-specific death rates from CNS vascular lesions in younger groups. However, one might reasonably expect such changes to affect both sexes equally. Because mortality in women has decreased much more than in men, we must also consider other explanations:

1. There may have been a true decrease in incidence of CNS vascular lesions, perhaps due to more effective treatment of underlying hypertension, while the case fatality rate remained the same.

2. The incidence of CNS vascular lesions may have remained about the same, but improved treatment of stroke patients could have reduced the case fatality rate. This improved treatment may have allowed survival into later years, when death results from recurrences of the cerebrovascular disease or from other causes. When a greater number of older patients with cerebrovascular accidents have had previous occurrences, or have other conditions which reduce their powers of recovery, mortality rates might reasonably increase in these older groups despite the improved treatment. In order to explain the sex difference, one can only suggest that women may respond better than men to the improved medical treatment.

CONCLUSIONS AND SUMMARY

Vascular lesions of the central nervous system are a relatively neglected field of study. By 1900, these lesions were diagnosed often, whereas coronary occlusion and myocardial infarction were rarely diagnosed before 1920. Many deaths which would have been attributed to "apoplexy" around 1900 may now be diagnosed as, or coded to, more recently emphasized types of heart disease.

Crude death rates from CNS vascular lesions have increased since 1939. Since 1949, age-specific rates have fallen more for younger persons than for older, more for women than for men, and more for whites than for non-whites. Changing diagnostic habits and improved treatment most likely have played the major part in causing these decreases.

Mortality rises with increasing age, is greater in white men than in white women of the same age, and is greater in non-whites than in whites. Since 1949, the increased emphasis on precise diagnosis has resulted in more frequent diagnoses of subarachnoid hemorrhage and of cerebral embolism and thrombosis, and fewer diagnoses of cerebral hemorrhage and "other and ill-defined lesions."

Like most mortality studies, this paper provides suggestive leads rather than definitive findings. Studies of the incidence of cerebrovascular lesions in a known population are much needed to supplement mortality information. From the epidemiologic point of view, such factors as age, sex, race, and time affect CNS vascular lesions in a different way from the total group of cardiovascular diseases. Additional epidemiologic studies are needed to clarify the reasons for mortality differences.

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THE EPIDEMIOLOGY OF CORONARY HEART DISEASE IN MIDDLESEX COUNTY, CONNECTICUT

I. A Preliminary Report on Methodology and the Incidence of Primary Myocardial Infarction

HENRY EISENBERG, M.D., M.P.H.,
WILLIAM R. FELTNER, M.D.,
GERALD H. PAYNE, M.D., AND
CHARLES A. HADDAD, B.S.

HARTFORD, CONN.

*From the Chronic Disease Control Section, State Department of Health, State of Connecticut**

(Received for publication April 28, 1960)

INVESTIGATIONS in the area of coronary heart disease have become more numerous in recent years. Estimates of incidence rates for selected groups have been provided by some studies. However, such estimates for unselected population groups have been very difficult to obtain. Zukel and associates[1] have recently presented some preliminary results from an epidemiologic study of coronary heart disease in the general population of a six-county area in North Dakota. This paper will describe a similar project in an area of the United States with higher mortality rates.† It is the first of a series of reports from the Middlesex County Coronary Heart Study and will be confined to a report of the development of the study, the methods used, the results of the efforts to obtain incidence and prevalence rates for coronary heart disease, and a brief evaluation of the physician-reporting method used in this study.

DEVELOPMENT

Preliminary conferences among interested groups—the Connecticut State Department of Health, the American and Connecticut Heart Associations, and the Public Health Service—were held in 1956. The specific objectives, the general methodology, and the feasibility of a proposed epidemiologic study were discussed. Comparison of different geopolitical units within the state resulted in the selection of Middlesex County as highly suitable for a study of this kind. The County had a population of approximately 75,600, or 3.4 per cent of the state's population by the 1956 estimate of the Connecticut Bureau of Vital Statistics.

The preliminary report was presented before the Epidemiology Section of the American Public Health Association on Oct. 19, 1959, in Atlantic City, N. J.

*In cooperation with the Connecticut Cardiovascular Disease Committee, Middlesex County, Conn.: Harold E. Speight, M.D., Chairman; Herbert Levine, M.D., Assistant Chairman; John J. Korab, M.D., Andrew F. Turano, M.D., and F. Erwin Tracy, M.D.

†In 1950 North Dakota had a crude death rate from arteriosclerotic and degenerative heart disease of 205.8 per 100,000; Connecticut had 322.3 per 100,000; and the United States, 269.5 per 100,000.[2]

One urban center, Middletown, had approximately 30,000 individuals in 1956 and one general hospital. The County is situated in the south-central portion of the state along the Connecticut River and the shore line (see map, Fig. 1). It has suburban and semirural areas and a farm population of approximately 5 per cent (1950 census). The population has a median age of 34 years (1950 census).

The approach to the problem and plan of study were discussed with the County Medical Society and the County Heart Association and their approval and cooperation were secured. A coordinating committee with members from the County Medical Society was formed. The belief that a voluntary reporting system for a specific disease would work in Connecticut was strengthened by the fact that for almost 25 years physicians of the state have contributed through all Connecticut general hospitals to a voluntary case-reporting and follow-up system of cancer cases. That system has worked so well that, with the inclusion of information regarding cancer on death certificates, the most reliable population-based incidence rates of cancer by site in this country have been obtained in Connecticut.

Soon after the beginning of the collection of cases, a meeting was held with representatives of the similar study in North Dakota in order to establish the same criteria of diagnoses and methods of follow-up to assure as nearly comparable data as possible.

Every effort was made to follow these criteria. North Dakota had a board of three internists review the cases histories and electrocardiograms; Connecticut had one cardiologist review all electrocardiograms and one public health internist and another physician from the Heart Disease Control Program review the case histories and all electrocardiogram reports. It is inevitable that, with different individuals making decisions in categorizing cases along a disease continuum, variation will occur.

AIMS

The study was first set up to answer some broad questions, as follows:

1. To attempt to determine incidence and prevalence of coronary heart disease in the general population of the County.

2. To find the relationships of the occurrence of coronary heart disease and factors of age, sex, race, national background, and other diseases.

3. To evaluate a physician-reporting method of epidemiologic investigation.

However, the project soon developed into a series of studies, interrelated in methodology and specifically involving nutritional and sociopsychological factors in myocardial infarction patients. The results of these additional investigations are outside the scope of this paper and will be discussed in later reports.

METHODS

Prior to Jan. 1, 1957, all general practitioners and internists in the County and 250 fringe area general practitioners, internists, and cardiologists were circularized with an introductory letter and reporting forms. An article in the

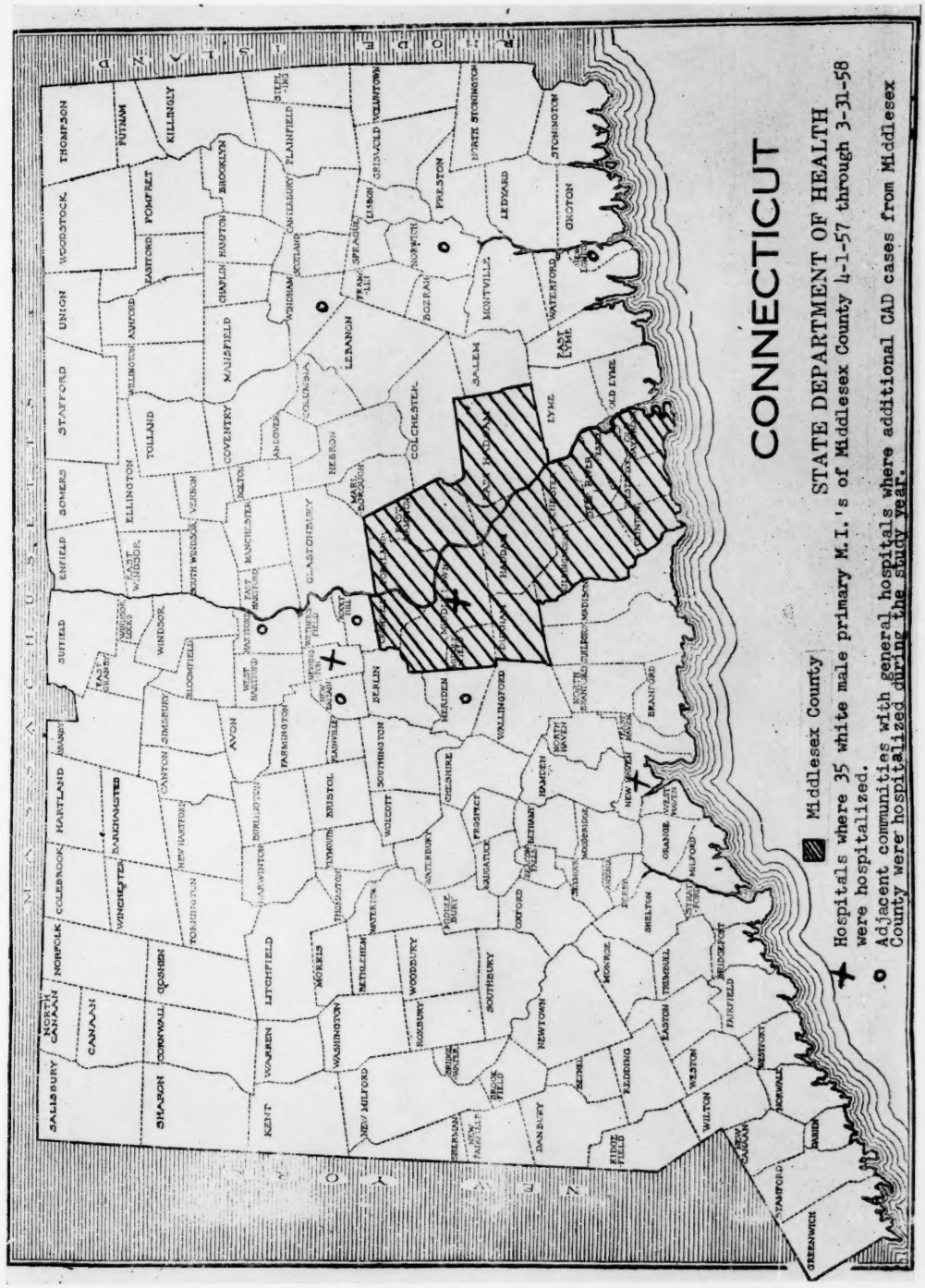
CONNECTICUT
STATE DEPARTMENT OF HEALTH
Middlesex County
Hospitals where 35 white male primary M.I.'s of Middlesex County 4-1-57 through 3-31-58 were hospitalized.
Adjacent communities with general hospitals where additional CAD cases from Middlesex County were hospitalized during the study year.
MASSACHUSETTS
NEW YORK
RHODE ISLAND

Fig. 1.

CONNECTICUT CARDIOVASCULAR DISEASE STUDY

PLEASE PRINT OR TYPE

1. _____ Physician _____ Town

2. _____ Patient's name Last First Middle _____ Age

_____ Patient's address _____ Town

Occupation _____ _____ Colored _____ Male

Race _____ White Sex _____ Female

Marital Status _____ Married _____ Widowed _____ Single _____ Divorced National Background _____

3. DIAGNOSIS

	Date of First Attack	Date of Current Attack	Certainty of Diagnosis: Certain	Certainty of Diagnosis: Probable
A. Coronary Artery Disease				
1. Angina Pectoris				
2. Coronary Insufficiency				
3. Myocardial infarction				
4. Other manifestations of Coronary Artery Disease				

5. ECG taken and available _____ Yes _____ No

6. Is this the first time coronary artery disease has been diagnosed in this individual? _____ Yes _____ No If yes, please see reverse side "A".

B. Cerebrovascular Accident

Type	Date of Attack
1. _____ Hemorrhage	
2. _____ Thrombosis	
3. _____ Embolism	
4. _____ Undetermined	

5. Did patient have hypertension? _____ Yes _____ No Usual BP _____

6. Has patient had previous cerebrovascular accidents? _____ No _____ Yes
When? _____

4. Did patient expire? _____ No _____ Yes
Was autopsy performed? _____ No _____ Yes

_____ Physician's Signature _____ Date

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OVER

Fig. 2.

Connecticut State Medical Journal further explained the study and brought the project to the attention of all physicians in the state. All hospitals in the County and in the fringe area likely to receive patients normally residing in the County were contacted and apprised of the study; arrangements were made with medical staffs and record librarians so that their records could be periodically reviewed by a United States Public Health Service physician working with the Study

A. Additional information on newly diagnosed cases of coronary artery disease:

1. What was patient doing when current attack occurred? _____

2. On basis of clinical findings how would you classify the current attack?

a) ____ Mild ____ Moderate ____ Severe

b) Presence of complications:

Shock _____ Arrythmia _____
Intractable pain _____ Embolism _____
Congestive heart failure _____ Other _____

3. Associated diseases present:

a) ____ Diabetes Mellitus
b) ____ Hypertension Usual BP before attack _____
c) ____ Obesity
d) ____ Other _____

4. May our nutritionist and sociologist call on the patient at his convenience for information on diet and socio-psychological background for epidemiological correlations? ____ Yes ____ No

Consultant's Opinion:

Comments:

ECG Report:

Chest X-Ray:

Fluoroscopic Report:

Fig. 2—*Continued.*

Committee to identify cases relevant to the study. The Bureau of Vital Statistics, Connecticut State Department of Health, agreed to supply us with a copy of all death certificates pertaining to Middlesex County, listing any type of heart disease or cardiovascular accident as the primary or contributing cause of death. To assist the County physicians involved, a physician from the study staff personally visited the general practitioners and internists every four to five weeks throughout the reporting phase of the study. He discussed with them reported cases, secured copies of electrocardiograms when available, or obtained information on cases as yet unreported but known to the study through hospital records or death certificates. The reporting form (Fig. 2) was made brief and permitted the reporting physician to categorize each case under the proper diagnosis. Other information requested included the date of first attack, the date

of current attack, certainty of diagnosis, and pertinent identifying and social data. Early in the reporting period, to encourage interest and cooperation and to further, indirectly, the principle of careful diagnostic procedures, a well-known pathologist from New York City, experienced in epidemiologic studies of coronary heart disease, gave a lecture at the County hospital to a large group of County physicians. He discussed the diagnosis and epidemiology of coronary heart disease.

CLASSIFICATION OF CASES

The classification of cases as angina pectoris, coronary insufficiency, and other manifestations of arteriosclerotic heart disease was done principally upon the basis of the reporting physician's diagnosis, though evaluation of their electrocardiographic diagnoses and clinical histories was made to find possible myocardial infarction cases reported under the less severe diagnostic categories. For reported cases of myocardial infarction every effort was made to obtain any laboratory and/or electrocardiographic evidence available from physicians and from hospital records. Serial tracings were particularly useful. Diagnoses on discharge were noted for any changes in the physician's final concept of the case. All electrocardiograms were reviewed by one cardiologist without knowledge or reference to clinical data (except age) about the patient. The following criteria were followed by the cardiologist in categorizing the electrocardiograms:

1. "Diagnostic myocardial infarction," when classical infarct patterns were present, consisting of abnormal Q waves, coved or elevated S-T segments, and symmetrically inverted T waves.

2. "Probable myocardial infarction," when there were definite elevations, such as elevated S-T segments, coved T waves, or abnormal Q waves which did not constitute a classical pattern.

3. "Suggestive of myocardial infarction," when there were borderline abnormalities of S-T segment, Q wave, or T wave, of the sort which, if more pronounced, would lead to a more definite diagnosis.

4. "Possible or compatible with but not diagnostic of myocardial infarction," when there were T changes only, with perhaps some suggestive S-T changes which were not diagnostic in themselves.

A team of physicians reviewed the clinical evidence for each case of primary myocardial infarction* among white males aged 35 to 64 years derived from the physician's reporting form and/or the electrocardiographic interpretations of the independent cardiologist. With consideration of all known factors for each case, this team categorized it as "definite," "probable," "possible," or "probably not" myocardial infarction. Only the first two categories were included for statistical analysis as myocardial infarction cases. The other two categories were included in the category of the more probable diagnosis for each case—usually coronary insufficiency. With regard to categorization, cases were designated as "definite" when the physician reported certainty of diagnosis and a characteristic history and the electrocardiogram was confirmatory or strongly suggestive.

*Primary myocardial infarction case refers to one with no previous history of a myocardial infarction though the patient may or may not have had angina or coronary insufficiency without infarction.

Cases were labeled "probable" when physicians were somewhat uncertain of the diagnosis, listing "probable myocardial infarction," "coronary insufficiency," or "angina," and ECG interpretations were "probable," or when the physician listed certain mild myocardial infarction but electrocardiographic interpretations were suggestive but not diagnostic or not available for review by the cardiologist. Cases resulting in death within a few hours after onset and before electrocardiograms could be obtained were categorized according to criteria set forth in 4, 5, 6, and 7 below.

The following classification of cases was followed in both the North Dakota Study and the Middlesex County, Connecticut, Study:

1. Angina (diagnosis of reporting physician accepted)
2. Coronary insufficiency
    a. Confirming ECG
    b. ECG does not confirm
    c. No ECG
3. Myocardial infarction
    a. Confirming ECG (prefer serial tracings)
    b. ECG does not confirm (prefer serial tracings)
    c. No ECG
4. Deaths attended by physician and signed out as myocardial infarction (or coronary occlusion) will be classified as definite coronary disease
5. Unattended death with definite coronary disease
    a. Autopsy showing acute changes—myocardial infarction and/or coronary occlusion
    b. History of coronary disease with definite symptoms immediately before death
6. Unattended death with probable coronary disease
    a. No history of coronary disease with symptoms suggestive of coronary disease immediately prior to death
    b. Past history of coronary disease, no known symptoms immediately prior to death
7. Unattended death—unknown cause (possible coronary disease) No history of coronary disease, no symptoms at time of death
8. Other manifestations of coronary disease

Each case is evaluated individually on the basis of ECG, the history, and whatever laboratory material is available.

The reporting period was extended to eighteen months, of which the middle twelve months—April, 1957, through March, 1958—have been used for statistical evaluation because it was found that reporting was obviously not complete during the first weeks of the study and it was anticipated that lag in reporting would have the same effect upon the last few weeks of reporting. Near the end of the reporting phase of this study, in order to define the general characteristics of the white male population, aged 35 to 64, in the County, the Bureau of the Census completed a health survey by trained interviewers who enumerated all persons and queried all white males of these ages living in a probability sample for one

out of every eight dwelling units in the County. This survey produced data as to personal characteristics, medical care, illnesses, symptoms, and other information pertinent to the other phases of the epidemiologic study. The same questionnaire was used in interviewing white males aged 35 to 64 with reported cases of primary myocardial infarction in the County or survivors of these persons.

RESULTS

During the eighteen months of the study ending June 30, 1958, 962 cases of coronary heart disease and/or cerebral vascular accident were reported to the Connecticut State Department of Health. Of these, a total of 342 cases had the specific diagnosis of angina, coronary insufficiency, myocardial infarction, or other manifestations of coronary heart disease made for the first time during the period from April 1, 1957, to March 31, 1958. The most adequate information was obtained for the 74 white males aged 35 to 64 who were reported to have had their first myocardial infarction in this twelve-month period.

The Bureau of Census Survey of the County resulted in the enumeration of 1,353 white males aged 35 to 64. Table I briefly describes certain findings in this survey. It should be realized that, of the 3,531 dwelling units selected for the survey, only groups "a" and "c" and 43 of the 46 in group "d" under "3" should be considered as unknowns, which would affect population estimates and possibly bias the estimates of the population characteristics. It has been assumed in the population estimates that these approximately 6.5 per cent unknown dwelling units would be proportionately distributed in a way similar to that of the 93.5 per cent known dwelling units with regard to age, race, and residence characteristics of the persons living there. The factor 1.068 under "6" in Table I reflects this assumption.

Table II presents the breakdown of the 74 cases of primary myocardial infarction among white males aged 35 to 64 and the decade-specific incidence rates based upon population estimates from the Bureau of the Census Survey. The diagnostic categories "definite" and "probable" are based upon criteria set forth in the Methods section. In the "not known dead"* group, 21 had definite ECG diagnoses† as well as definite clinical diagnoses of myocardial infarction, though one of the clinical diagnoses was made in retrospect. Seven others had definite clinical diagnoses of myocardial infarction and suggestive or probable myocardial infarction electrocardiographic diagnoses. Two had clinical diagnoses of definite mild myocardial infarction and ECG diagnoses of uncertain but possible myocardial infarction and 2 had definite or probable clinical diagnoses of myocardial infarction but the ECG's taken were not available for the independent cardiologists to review. These 10 cases are listed as "probable MI." In the nonsurviving group, 5 had definite clinical diagnoses and definite ECG diagnoses. The 5

*"Not known dead" is used instead of "living" because follow-up to physicians and checking of death certificates in the Connecticut Bureau of Vital Statistics have failed to establish the vital status of 10 of the 38 not known to have died within a year after this first MI. Four of these 38 (one in the age group 35 to 44, one in 45 to 54, and 2 in 55 to 64) are known to have died 21, 26, and 28 (2 cases) months after their first MI.

†ECG diagnoses refer to the diagnoses made by the independent cardiologist reviewing the records available for these cases.

TABLE I. DATA OBTAINED BY THE BUREAU OF THE CENSUS FOR POPULATION ESTIMATES IN MIDDLESEX COUNTY, CONNECTICUT, 1958*

1. Approximate number of total dwelling units (8 times the randomly selected sample)		28,248
2. No. of dwelling units selected		3,531
3. No. of dwelling units without responding County residents		1,020
a. Refusals	67	
b. Vacant, inhabited by nonresident, or in Armed Forces	789	
c. No one at home, temporary absence	118	
d. Miscellaneous reasons	46	
4. No. of households with responding County residents		2,511
5. No. of non-white households		35
6. No. of white households with no white male aged 35 to 64		1,164
7. No. of households with one or more white males aged 35 to 64		1,312
8. No. of white males, aged 35 to 64, interviewed		1,353
9. Population estimate for white males aged 35 to 64 in Middlesex County, Connecticut		11,559

*1,353 × 8† × 1.068.‡

†Because sample was 1/8 of population of white males aged 35 to 64.

‡Factor to correct for the less than 7 per cent of dwellings where no information about presence or absence of white males aged 35 to 64 could be obtained and for which the assumption was made that the distribution would be similar to that for the known 93+ per cent of the sample.

autopsied cases had confirming evidence of acute MI. For one additional case an ECG was suggestive and the clinical diagnosis certain. An ECG for another man was reported as "probable MI" but was not available for review by the independent cardiologist. This man died of mesenteric thrombosis a few months later but no autopsy was allowed. Six patients died with physicians in attendance but before ECG records could be made. Clinical diagnoses were "definite MI." These 18 cases are designated "definite MI—known dead." Fourteen additional persons had prior symptoms of coronary heart disease and/or terminal symptoms typical or strongly suggestive of MI observed by a responsible adult but not by a physician. These are designated in Table II as "probable MI—sudden death with information." Four persons with an available previous history and unknown terminal symptoms but with death certificate diagnosis of "acute MI" or "coronary occlusion" are included under "probable MI—sudden death with no information." The electrocardiographic and autopsy findings which were weighed heavily in determining "definite" or "probable" status for these 74 primary myocardial infarctions in white males are summarized in Table III.

EVALUATION OF METHOD

In reviewing the approach used in seeking the cooperation of the practicing physicians to report voluntarily cases of coronary heart disease, we can recommend that it be used only when certain circumstances prevail. Of the utmost importance is the whole-hearted continuous cooperation of the private practitioners involved, not only those within the County, but also those in the adjacent areas. A high degree of motivation must exist within the medical profession in

TABLE II. INCIDENCE RATES PER 1,000 POPULATION FOR PRIMARY MYOCARDIAL INFARCTIONS, DEFINITE OR PROBABLE, IN WHITE MALES, AGED 35 TO 64, MIDDLESEX COUNTY, CONNECTICUT

	TOTAL			DEFINITE MI		PROBABLE MI		
	ALL CASES	DEFINITE MI	PROBABLE MI	NOT KNOWN DEAD	KNOWN DEAD*	NOT KNOWN DEAD	SUDDEN DEATH WITH INFORMATION	SUDDEN DEATH WITH NO INFORMATION
Ages 35-44 (Pop. est. 4,639)								
No. of cases	9	7	2	6	1	1	0	1
Incidence rate	1.9							
Ages 45-54 (Pop. est. 4,152)								
No. of cases	26	13	13	6	7	6	5	2
Incidence rate	6.3							
Ages 55-64 (Pop. est. 2,768)								
No. of cases	39	26	13	16	10	3	9	1
Incidence rate	14.0							
Total: Ages 35-64 (Pop. est. 11,559)								
No. of cases	74	46	28	28	18	10	14	4
Incidence rate	6.4	4.0	2.4					

*Reports of deaths received from the State Bureau of Vital Statistics through March, 1959.

TABLE III. INCIDENCE OF PRIMARY MYOCARDIAL INFARCTIONS OCCURRING IN WHITE MALES, AGED 35 TO 64, MIDDLESEX COUNTY, CONNECTICUT, APRIL, 1957, TO MARCH, 1958, BY FINDINGS OF ELECTROCARDIOGRAMS AND AUTOPSIES

	TOTAL CASES	NOT KNOWN DEAD	KNOWN DEAD
Ages 35-44 (Pop. 4,672)			
Confirming ECG	6	6	0
Suggestive ECG	1	1	0
Confirming autopsy	0	0	0
No ECG or autopsy	2	0	2
Total	9	7	2
Ages 45-54 (Pop. 4,144)			
Confirming ECG	7	6	1
Suggestive ECG	5	4	1
Confirming autopsy	4	0	4
No ECG or autopsy	10	2	8
Total	26	12	14
Ages 55-64 (Pop. 2,776)			
Confirming ECG	21	17	4
Suggestive ECG	4	2	2
Confirming autopsy	1	0	1
No ECG or autopsy	13	0	13
Total	39	19	20
Total: Ages 35-64 (Pop. 11,592)			
Confirming ECG	34	29	5
Suggestive ECG	12	9	3
Confirming autopsy	4	0	4
No ECG or autopsy	24	0	24
Total	74	38	36

these areas. A plan of uninterrupted stimulation to participants starting prior to the onset of the reporting phase and continuing throughout it must be carefully devised and executed. Moreover, well-trained professional persons, not necessarily physicians, should be available to be in frequent contact with the medical profession in their offices and their hospitals. Cooperative working arrangements in record rooms and cardiology laboratories in the hospitals of the reporting and adjacent areas must be established. Only in this fashion do we believe that this methodology will give as nearly complete reporting as one could expect from any population study.

In an evaluation of this method it is important to reveal the percentage of cases which could have been obtained by checking hospitals and death certificates only and not involving the physicians in the primary reporting phase. Thirteen of the 74 patients, or 17.6 per cent, were not hospitalized and these cases did not appear among death certificates at the Connecticut Bureau of Vital Statistics within 1 year after the study year. It might be anticipated that in other areas

where hospital facilities are more centrally located or more readily accessible to all residents of the area than in Middlesex County (Fig. 1) this percentage of nonhospitalized patients who survived primary myocardial infarction would be smaller. There was a clumping of nonhospitalized patients in the southeastern section of the County which is farthest from hospital facilities. Four of the 74 patients, 5.4 per cent, were hospitalized in adjacent area hospitals and 2 were hospitalized and died out of state and were identified, one by a Middlesex County physician and one by death certificate alone.

DISCUSSION

The number of cases reported for the other categories of coronary artery disease than myocardial infarction, that is, as angina, coronary insufficiency, and other manifestations, are probably not so nearly complete as for myocardial infarction. By the nature of the technique of physician reporting and a system of checks through examination of hospital records and death certificates we are aware that cases with the more serious manifestations have been rather exhaustively sought; whereas the knowledge of instances of less serious manifestations has been dependent upon the individual and collective motivation, memories, and cooperation of the nearly 150 participating physicians in Middlesex County and the adjacent area. The types of record checks and physician interviews necessary to obtain more accurate data with regard to incidence and prevalence rates of these other categories and prevalence rates for myocardial infarction were not within the scope of personnel and budgetary limits of this study.

In light of the criteria used to determine cases of myocardial infarction, that is, clinical diagnosis, electrocardiographic interpretation by an independent cardiologist, and any other laboratory data available for a specific case, it is desirable to present more than one incidence rate for primary myocardial infarction among white males aged 35 to 64 in Middlesex County, Connecticut (Table IV). For those cases reported during the twelve-month period from April 1, 1957, to March 31, 1958, with designation of definite myocardial infarction, an incidence rate of 4.0 per 1,000 was obtained. If, on the other hand, one includes three additional groups of cases—first, the sudden deaths for which information as to the symptomatology prior to the death was available; second, the sudden deaths for which information was not available; and third, those cases without known death, but which because of a discrepancy in either definite symptomatology or electrocardiographic evidence have been described as probable myocardial infarction—the inclusion of all these cases produces an incidence rate of 6.4 per 1,000.

If we exclude from this total those sudden deaths without information and those not known to be dead which have been labeled "probable," an incidence rate of 5.2 per 1,000 is obtained. We conclude, therefore, that 5.2 is the minimal rate which applied to the Middlesex County study because it now includes only cases with definite symptoms of infarction or definite changes of myocardial infarction in the electrocardiogram or confirming autopsy findings.

The reviewing physicians felt that among the cases excluded from the minimal rate are several which would have been designated as definite myo-

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TABLE IV. CORONARY HEART DISEASE AND CEREBROVASCULAR ACCIDENT CASES REPORTED FROM JAN. 1, 1957, TO JUNE 30, 1958

Total all ages: 962. *CHD only:* 672. *CVA only:* 250. *CVA and CHD:* 40.

CASES OF MYOCARDIAL INFARCTION, CORONARY INSUFFICIENCY, ANGINA, OR OTHER MANIFESTATIONS FROM APRIL 1, 1957, TO MARCH 31, 1958, BY AGE AND SEX

	TOTAL CASES	UNDER 35	35-44	45-54	55-64	65-74	75-84	85+	UNKNOWN
First MI									
Male	149	0	9	26	39	40	24	11	0
Female	83	0	2	4	14	33	19	10	1
Total	232	0	11	30	53	73	43	21	1
First CI (No MI)									
Male	27	0	3	7	5	6	2	4	0
Female	15	0	0	5	5	1	3	1	0
Total	42	0	3	12	10	7	5	5	0
First Angina (No MI or CI)									
Male	19	2	1	3	6	6	1	0	0
Female	10	0	0	2	3	4	0	1	0
Total	29	2	1	5	9	10	1	1	0
Other Manifestations of CHD for First Time (No MI, CI, or Angina)									
Male	22	0	0	0	4	9	6	3	0
Female	17	0	0	0	2	2	6	7	0
Total	39	0	0	0	6	11	12	10	0
Grant Total									
Male	217	2	13	36	54	61	33	18	0
Female	125	0	2	11	24	40	28	19	1
Total	342	2	15	47	78	101	61	37	1

cardial infarctions if additional electrocardiograms or autopsies had been obtainable. Hence, a more nearly accurate rate in this respect lies somewhere between the minimal 5.2 and the more inclusive rate of 6.4. We are aware that even in the rate of 6.4 all of the so-called silent infarctions are not included. According to a report from the Framingham study[3] unrecognized myocardial infarction (silent coronaries) amounted to 21 per cent of their cases. If this percentage were added to our minimal rate, the rate for myocardial infarction in white males aged 35 to 64 years would be approximately 6.3 per 1,000.

The question arises as to how the incidence rate for myocardial infarction in Middlesex County, Connecticut, compares with that found in North Dakota in the six-county area study where a similar approach was used. A review of their data with age adjustment to that of the Middlesex population reveals that their incidence rate for primary myocardial infarction for white males aged 35 to 64 was only 3.3 per 1,000 (Table V). However, 52 per cent of their population is engaged in farming. This is not the case in Middlesex County where the farm

TABLE V. COMPARISON OF INCIDENCE RATES FOR PRIMARY MYOCARDIAL INFARCTION IN WHITE MALES, AGED 35 TO 64, IN MIDDLESEX COUNTY, CONNECTICUT, AND SIX-COUNTY AREA IN NORTH DAKOTA

	INCIDENCE	POPULATION ESTIMATE	NO. OF CASES
Middlesex County, Connecticut			
1. Incidence rate Including:			
Definite myocardial infarction	4.0/1,000	11,559	46
Probable myocardial infarction	2.4/1,000	11,559	28
Total	6.4/1,000	11,559	74
2. Incidence rate as in 1 but excluding:			
Probable cases not known dead, and			(10)
Cases of sudden death with no terminal information available			(4)
Minimal incidence rate	5.2/1,000	11,559	60
3. Incidence rate as in 1 but excluding:			
Cases of sudden death with no terminal information available			(4)
Those known to have had symptoms of coronary heart disease prior to the study year			(9)
Incidence rate comparable to that of North Dakota	5.4/1,000	11,559	61
Six-County Area of North Dakota			
1. Incidence rate of primary myocardial infarction without previous symptoms	3.3/1,000*	15,360	53 (50.2)†
2. Incidence rate, excluding farmers	4.4/1,000*	7,280	32 (32.1)†

*Age adjusted to that of Middlesex County, Connecticut, population (1958 estimate).
†Expected number of cases when North Dakota population age was adjusted to that of Connecticut.

population is small (approximately 5 per cent). None of the 74 individuals with primary myocardial infarction of this age group in Connecticut were farmers or farm laborers. In the North Dakota study there is an apparent difference in the rates for primary myocardial infarction among farmers (adjusted rate 2.2 per 1,000), and other occupational groups (4.4 per 1,000). Therefore, it seems more reasonable in any comparison of the occurrence of primary myocardial infarction in these population groups to use only the nonfarm population of North Dakota. The rates to be compared then are 4.4 per 1,000 for the six-county area of North Dakota, excluding farmers, and 5.3 per 1,000 for Middlesex County, Connecticut (these exclude cases of sudden death without information and cases with previous symptoms of coronary heart disease occurring before the reporting year). This difference is not demonstrated to be statistically significant. In a more comprehensive comparison study of the data from the two studies other factors to explain differences in rate may also emerge.

SUMMARY

1. This report contains a description of the methodology of voluntary reporting of coronary heart disease by private physicians in a general population group in Middlesex County, Connecticut, during an eighteen-month reporting period.

2. Under the most favorable conditions of cooperation and motivation of the practicing physicians and by the effective coordination of a full-time professional staff, such an approach did, as expected, produce valuable information.

3. Population estimates made from the United States Bureau of the Census interview data collected on a probability sample of the population of the County made it possible to determine incidence rates for primary myocardial infarction among white males, aged 35 to 64, for the year April, 1957, through March, 1958. It was concluded that a minimal incidence rate (for myocardial infarction among white males aged 35 to 64 for Middlesex County, Connecticut) was 5.2 per 1,000 and that the actual rate was somewhat larger—approximately 6 per 1,000.

4. Comparisons with similarly obtained data in North Dakota were presented. The rate in Middlesex County for cases comparable to those cases included in the North Dakota rate is significantly higher (5.4 to 3.3) when all the six-county area population in North Dakota is included and not significantly higher (5.3 to 4.4) when the farmers are excluded from the North Dakota population.

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Pathobiology

ABNORMAL TRACE METALS IN MAN: CADMIUM

HENRY A. SCHROEDER, M.D., AND J. J. BALASSA, PH.D.

BRATTLEBORO, VT.

WITH THE TECHNICAL ASSISTANCE OF JEAN C. HOGENCAMP, B.S.

From the Department of Physiology, Dartmouth Medical School, and the Brattleboro Retreat

(Received for publication Sept. 24, 1960)

CADMIUM, usually considered a toxic metal, and under certain circumstances a nephrotoxic one, has been found in the kidneys of all adult human beings from many cities of the world.[1,2] Its concentrations were highest in Japanese and lowest in African natives.[2] Its virtual absence in the newborn and its accumulation with age[1] have made this trace metal of unusual interest, even to the point of speculation that it may represent one factor affecting longevity and causing chronic disease in older persons. Little, however, is known of its biologic activity, if any; whether or not it is a trace metal essential for health; whether or not it is ubiquitous in natural foods; whether or not it represents an industrial contaminant. Studies in the past have been mainly concerned with cadmium as a toxic material unsuitable for lining food containers, interest in such a possible use having arisen under economic pressure when tin supplies were short during time of war (1920, 1940).[3,4,5] Klein and Wichmann,[6] in developing an analytical method, found cadmium in a few foods and biologic materials.

The purpose of the present investigation has been to attempt to answer two questions: (1) What are the major sources of the renal cadimum found in human beings? (2) Are these sources "natural" or has cadmium been introduced into foods and beverages as an industrial contaminant? A third and important question concerning its biologic activity cannot be answered until long-term experiments in mammals are completed.

According to recent estimates from spectrographic methods, approximately 30 mg. of cadmium is present in the "Standard American Man," of which about 10 mg. is in the kidneys and 4.1 in the liver.[7] Although it was found in every adult kidney and liver examined, other organs and tissues may or may not contain it.[1,8] The mean renal concentrations in two large series of American cases were 32 mg. per kilogram[1] and 51 mg. per kilogram wet weight,[9] with values for zinc of 48 and 94.6 mg. per kilogram, respectively.

As a basis for study, the extensive analyses of Tipton and her co-workers[1] offer the largest series available; their raw data were examined statistically.

Supported by grant-in-aid No. H-5076 from the National Heart Institute, Public Health Service.

Foods, beverages, and other materials were analyzed. In order to discover whether or not mammalian renal cadmium came from industrial products, the kidneys and livers of wild deer and other animals were examined. Two of the questions posed previously were thereby partly answered.

ANALYTICAL METHODS

Initially, samples of 5 to 20 Gm., depending upon estimated amounts of cadmium, were wet ashed with concentrated H_2SO_4 and HNO_3 until a colorless or clear yellow solution was obtained. The color was removed with 1 to 2 ml. 70 per cent $HClO_4$ heated to white fumes and driven off. Samples of water of 1.0 L. volume were evaporated to dryness and ashed.

Dry ashing of 2 to 100 Gm. samples was later done in a silica-lined electric muffle furnace in covered fused silica crucibles. After these were dried to constant weight at 110° C., the temperature was slowly raised to 450° C. for 24 hours. If ash was colored, 2 to 5 ml. of 40 per cent $Al(NO_3)_3 \cdot 9\ H_2O$ was added, evaporated to dryness, and reashed. If still not pure white, 5 to 10 ml. concentrated HNO_3 was added, evaporated, and the sample reashed.

Cadmium was measured by the dithizone method of Saltzman.[10] The only modification found necessary was the addition of extra sodium potassium tartrate to samples containing large amounts of calcium and magnesium, which on neutralizing precipitated in the funnel. Saltzman found his method sensitive to 0.05 μg Cd; known amounts of 1 to 5 μg added at frequent intervals to unashed samples in order to check the method showed recoveries with similar sensitivities.* Standard concentration curves obtained with a Bausch and Lomb Spectronic 20 Colorimeter gave straight line absorbance to 8.0 μg. No Cd was detected in any of the reagents used.

In 10 instances pairs of samples were ashed by wet and by dry techniques. Analyses on the ashes showed results comparable well within the analytical error in each case, with a mean difference of less than 5 per cent. Therefore, errors due to the method of ashing were minimal.

CADMIUM IN RELATION TO AGE

In Figs. 1 to 3 are shown the variations of cadmium in American kidneys and livers with age, according to spectrographic analyses.[1] The correlation ratios for renal and hepatic cadmium and zinc were significant statistically by the F test[11] ($p < 0.01$). These curves made from spectrographic analyses assume absence of cadmium in the newborn[1,12,13]; by chemical methods Voinar[14] detected very small amounts in Russian human fetuses. Spectrographic methods are less sensitive and usually detected none (Table I).

CADMIUM IN FOOD AND WATER

Food.—The concentrations of cadmium in 108 samples of food are given in

*If, as happened occasionally in early stages with this method, sensitivity by recovery experiments on a series of several analyses was less (0.1 or rarely 0.2 μg), the result on low values is indicated in the tables.

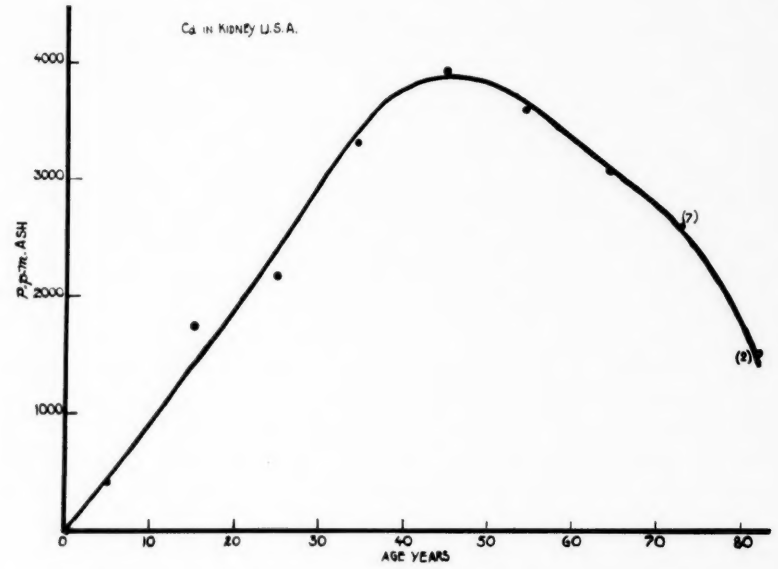

Fig. 1.—Mean level of cadmium in human kidney by decade, United States values, 201 cases, from data of Professor Isabel H. Tipton and others.[2] Coefficients of correlation: E = 0.7039; SE_E = 0.035, $p < 0.001$; r = 0.5587, $p < 0.001$.

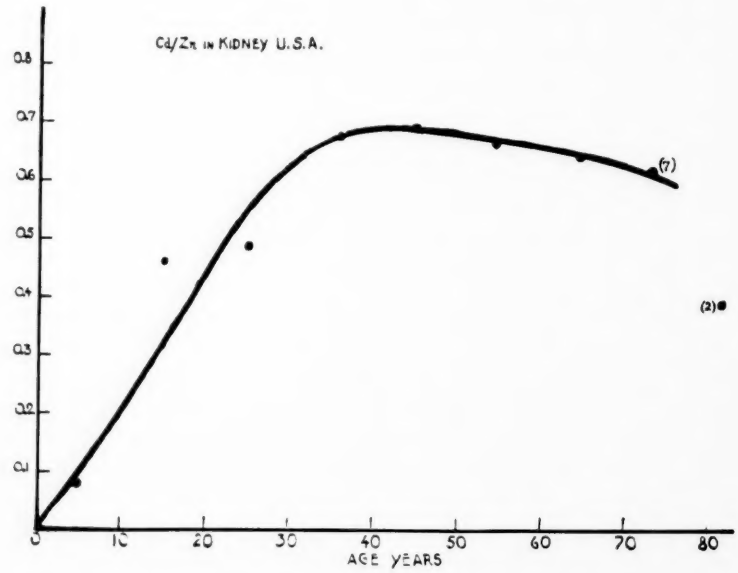

Fig. 2.—Ratio of cadmium to zinc in human kidney by decade, United States values, 201 cases, from data of Professor Isabel H. Tipton and others.[2] Correlation ratio for zinc: E = 0.1550, SE_E = 0.0597, $p < 0.01$. The curve of concentration of zinc rises more slowly before and falls more rapidly after age 45 than that of cadmium. Note that through most of adult life the concentration of cadmium approximates two-thirds that of zinc.

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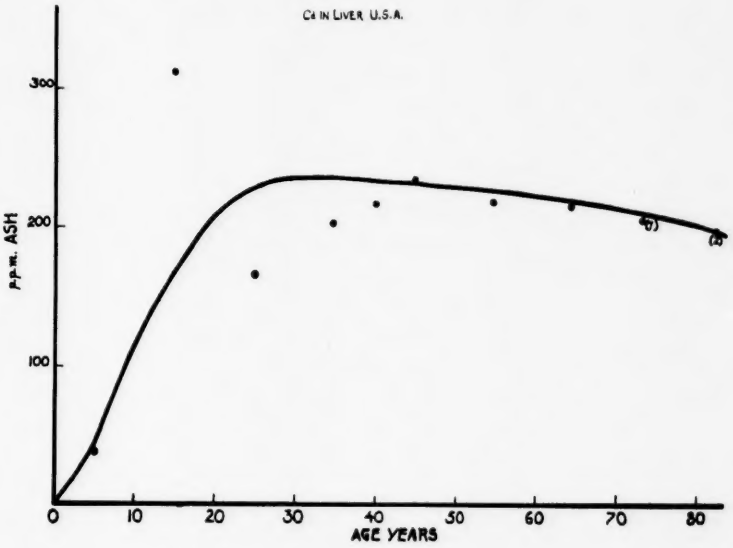

Fig. 3.—Mean level of cadmium in human liver by decade, United States values, 169 cases, from data of Professor Isabel H. Tipton and others.[2] Correlation ratio: E = 0.361, SE_E = 0.061, $p < 0.005$. Zinc in liver was more than 10 to 30 times the concentration of cadmium at all ages, decreasing by a third in the first two decades and varying little after age 25.

Table II, including 10 reported previously.[6] Amounts are indicated per 100 calories and per 100 Gm. of food. Little or none was found in most condiments and beverages, with the exception of evaporated milk and a cola drink. Mollusca and Crustacea contained large quantities. Appreciable amounts were found in all grains and grain products except rye, local corn, and one breakfast food. As expected, kidneys showed much cadmium. Among fresh or dried fruits and vegetables, concentrations were low or negligible except for two of the five legumes, two of the brassicas, and three greens. Peanuts and one brand of cigarettes contained large amounts. There was a suggestion in the data that some processed foods had more cadmium than similar raw foods, notably in the case of tomatoes, molasses, milk, and frozen corn, but, on the other hand, many tinned foods had little or none.

Water.—Cadmium was found in appreciable but small amounts in a number of water samples in contact overnight with galvanized iron pipes. It was not usually detected when the waters were fresh, i.e., were run for several minutes in order to clear the pipes. Water from natural, unpiped sources sometimes contained small amounts: the Connecticut River, two town reservoirs, a spring, and a brook, all in the local area (Table III). The consequences of rebuilding a forest spring and using black polyethylene pipe are indicated at the end of Table III.

Short sections of copper, black polyethylene, and galvanized iron pipes were immersed in a natural soft spring water of pH 5.8 to 6.0 for several days without stirring. Cadmium entered the water from both the galvanized (5.2 ppb) and the plastic pipe (5.0 ppb) while much copper was dissolved from the

copper pipe (Table IV). The influence of water at various pH's on copper piping is also shown in Table IV. The amounts of both metals dissolved were relatively large under laboratory conditions and the metal pipes were visibly corroded. Cadmium was also dissolved from laboratory rubber stoppers (5.5 ppb).

CADMIUM IN MAMMALIAN KIDNEYS

The great variations of concentrations in 8 mammalian and 3 avian kidneys are shown in Table V. While the influence of age cannot be evaluated, presumably the kidneys of livestock were from young mature animals. The ages of the deer were from 2 to 6 years or more, as estimated by antler "points." The human kidney and liver had the largest amount (except for the grouse); at age 0 to 12 years, the mean renal value of approximately 4 μg per gram[2] greatly exceeded that of beef and hogs and approximated that of wild mammals. Lamb and veal showed little. The high values in the squirrel and grouse are noteworthy.

SOURCES OF CADMIUM IN ANIMALS

Attempts to find common sources of renal cadmium in animals are shown in Table VI. Hay, grains (Table II), prepared foods may account for its presence in domestic animals; drinking water obviously contributed little (Table III). In the kidney and liver of wild deer, sources appeared to be the buds, twigs, bark, and needles of their usual winter forage, evergreen trees, and of one deciduous tree, the apple. Presumably these and similar sources contributed to the cadmium found in other wild animals and birds.

Direct or indirect exposure of laboratory animals to cadmium in materials other than foods is also indicated in Table VI. Cadmium was found in most of the material commonly used for bedding and in some material which could be so used. It was not detected in only two. Most manufactured substances used in laboratory buildings contained cadmium, while a few were free of the element. Diatomaceous earth (Celite), plastic tapes, black polyethylene, black rubber had considerable cadmium which, in the cases of the last two, dissolved in soft water (Table IV).

The absence of cadmium in one grain, rye, and hay from a field which had been limed but never fertilized, led to analyses of commercial fertilizers. All contained large amounts. The phosphate fraction of fertilizer appeared to have most if not all of the metal. One sample of phosphate rock from Tennessee had a relatively small amount, while phosphates from Florida showed high levels. Freshly dropped manure from dry cows eating cadmium-containing hay and beet pulp showed cadmium.

CADMIUM IN JAPANESE FOODS

The mean concentration of renal cadmium in 18 Japanese kidneys by spectrographic methods was 6,030 ppm ash (standard error $\pm$ 800), with a range of 1,350 to 19,500 ppm, roughly twice that found in American adult kidneys. In livers it was 540 ppm ash (S. E. $\pm$ 90) with a range of 100 to 1,550 ppm or three

times American values.[8]* From available data there seems to be little doubt that concentrations are higher in Orientals than in Indo-Europeans and Africans. It was necessary, therefore, to discover sources. The average Japanese diet of about 2,000 calories consists of 69 Gm. protein (22 Gm. of animal source), 20 Gm. fat, and 400 Gm. carbohydrate,[15] most of the last in the form of rice. Analyses of tea, rice, and flour are given in Table VII. Some local geographical variations may be present, but the amounts found were considerably higher than that in American rice.

DISCUSSION

The present study is the first of a series on the presence, sources, and biologic effects of certain "abnormal" trace metals in man. At present, for the purposes of this investigation, a trace metal is arbitrarily considered "abnormal" if it has no known biologic function, is not now believed to be essential for mammals, and is present in the tissues of man in easily detectable amounts. Changes of some of these metals to the essential group are probable in the near future.

In the "American Standard Man" appear some metals in larger amounts than might be suspected from knowledge of the natural environment.[7] Lead, tin, cadmium, barium, titanium, nickel are present in concentrations higher than others thought to be essential, such as molybdenum, cobalt, chromium, and possibly vanadium, while organ or tissue specificities are exhibited by aluminum, barium, cadmium, lead, chromium, strontium, titanium, and tin, all of which were found in all adult human beings. Therefore, it becomes necessary to discover sources of those metals without known biologic functions or with known toxicities, and to decide whether or not they are natural or artificial environmental contaminants or serve a useful purpose.

Estimated Balances of Cadmium.—The total bodily content of cadmium in the "American Standard Man" is estimated at 30 mg.,[7] with about a third in the kidneys. According to Perry and Perry[16] the urinary excretion varies widely but averages less than 12.7 μg per liter (range 22 to <7 μg), or a mean daily excretion rate of 17.9 μg (range 31 to <12 μg). At the very least, in order to accumulate 30 mg. in 30 years, 1,000 μg per year or roughly 3 μg per day must be retained above the amount excreted. Nothing is known of the proportion ingested which is absorbed from the intestinal tract of man. If all is absorbed, and the urine is the sole route of excretion, one can calculate roughly that 15 to 34 μg must be ingested daily, of which 10 to 20 per cent is retained.

Calculations of a basic 2,300 calorie diet of fresh foods containing 100 Gm. protein, 250 Gm. carbohydrate, and 100 Gm. fat from Table II, including flour and other grains as the main carbohydrate foods, would yield roughly 23 μg Cd per day. If seafoods and processed foods and beverages were used exclusively the cadmium content might approach 60 μg per day. If oysters and kidneys

*American renal levels were 2,800 ppm ash (range, 550 to 8,000), and hepatic levels 180 ppm ash (range, 50 to 1,500).[1] For comparison, the following levels can be quoted (mean, ± standard error) in ppm ash[2]: Hong Kong Chinese, 5,620 ± 950, Bangkok Thai 4,910 ± 1,470, Taiwan Chinese 4,150 ± 1,160, Bern Swiss 2,260 ± 480, Delhi-Lucknow Indians 2,120 ± 310, Nigerian Negro 1,700 ± 150, Ruanda-Urundi Negro 710 ± 150.

TABLE I. CADMIUM IN INFANTS AND CHILDREN (PPM ASH)

AREA	KIDNEY				LIVER				METHOD*	AUTHOR
	NO. SUBJECTS	NO. POSITIVE	CONC.	RANGE	NO. SUBJECTS	NO. POSITIVE	CONC.	RANGE		
Newborn.—										
England (term)	5	1	20		6	1	40		Spect.	Stitch[13]
U.S.A. (0-45 days)	16	0	—		16	0	—		Spect.	Tipton[1]
U.S.S.R. (fetus 4-9 months)	6	6	3.69	0.4–6.4		6	7.48	2.9–16.5	Chem.	Voinar[14]
Children to 11 years.—										
England	11	11	>600	0–>1,000	10	10	173	0–1,000	Spect.	Stitch[13]
U.S.A.	30	16	66	0–2,100	30	10	<50	0–230	Spect.	Tipton[1]
U.S.S.R. (4 years)	1	1	5		1	1	35		Spect.	Voinar[14]

*Spect., Spectrographic method.
Chem., Microchemical method.

TABLE II. CADMIUM CONTENT OF FOODS AND BEVERAGES

SAMPLE	VARIETY	SIZE (GM. OR ML.)	CD FOUND (μG)	CD PER 100 CALORIES*	CD PER 100 GM.	REMARKS
Condiments.—						
Salt, No. 1	Iodized	8.0†	0.05	—	Negl.‡	
Salt, No. 2	Iodized	10.0	0	—	0	
Salt, sea	Cape Cod	8.0†	0	—	0	
Pepper	Black	2.0†	0.2	—	Trace§	
Sugar, No. 1	White cane	4.0†	0.15	—	Trace§	
Sugar, No. 2	White cane	10.0	0.1	—	Trace§	
Vinegar	Cider	50.7	0.15	—	Trace§	
Baking powder		5.2	0.35	—	6.72	
Yeast	Dry	5.9	0.15	—	2.5	
Molasses	New Orleans	12.03	0.70	1.98	5.82	
Maple syrup		15.0†	0.2	—	0	Ref. 6
Beverages.—						
Tea	Black	4.0†	0.2	—	Trace§	Cf. Table VII
Tea	Green	2.0†	0.4	—	20.0	
Cocoa, No. 1		3.9	1.0	5.7	25.6	
Cocoa, No. 2		8.0	0.2	1.3	6.0	
Coffee	Ground	4.0†	0.05	—	Negl.‡	
Coffee	Instant	1.4	0.1	—	Trace§	
Ginger ale		40.0†	0.1	—	Trace§	
Birch beer		150.0	0.08	—	Negl.‡	
Cola, No. 1		40.0†	0.6	2.7	15/L.	
Cola, No. 2		77.0†	0.15	—	Trace§	
Milk, fresh, No. 1	Local	100.0	0.15	—	Trace§	
Milk, fresh, No. 2	Local	103.4	0.375	0.53	3.75/L.	
Milk, fresh		10.0	0.2	—	0	Ref. 6
Milk, evaporated, No. 1		40.0†	1.60	2.4	20/L.	Diluted
Milk, evaporated, No. 2		20.0†	0.35	1.1	8.8/L.	Diluted
Milk, dried, skim		1.8	0	—	0	
Milk, dried, skim†		5.0†	0.5	2.5	10/L.	Ref. 6
Beer, tinned		103.0	0.15	—	Trace§	
Sea Foods.—						
Oysters, fresh, No. 1	Cape Cod	10.0†	6.05	115.8	60.5	
Oysters, fresh, No. 2	Cape Cod	10.0†	7.15	139.0	71.5	Half dozen
Oysters, tinned	American	3.0	4.80	308.8	159.8	
Oysters, tinned		10.0	12.1	—	121.0	Ref. 6
Clams, hard, fresh	New England	12.5	2.35	39.5	18.8	
Mussels, fresh	Sea (N. H.)	20.5	2.95	22.1	14.7	
Crabmeat, tinned	Japan	20.0†	2.45	9.60	12.25	
Shrimps, fresh cooked	U. S. A.	7.1	0.7	8.8	10.0	
Lobster, fresh	Maine					
Claw		7.1	0.72	8.6	10.1	
Tail		3.0	0.40	11.2	13.2	
Digestive gland		17.4	26.85	—	154.0	
Herring, tinned	Norway	3.5	0.1	—	Negl.‡	
Salmon, tinned	Alaska	14.6	0.25	0.72	1.71	
Sardines, tinned	Norway	4.3	0.45	4.48	11.2	
Tuna, tinned	Oregon	11.4	0.7	2.37	6.2	
Swordfish, fresh	U. S. A.	11.13	0.45	1.41	3.7	
Anchovies, tinned	Portugal	6.1	0.1	—	Negl.‡	
Grains.—						
Wheat, winter seed	Treated	43.6	2.63	—	5.7	
Wheat, stone ground	Vermont	4.9	0.63	3.71	13.0	
Wheat, crushed	Vermont	13.3	1.50	3.70	12.9	
Flour, No. 1	Minneapolis	20.0†	1.75	2.50	8.75	Cf. Table VII
Flour, No. 1	Minneapolis	4.0†	0.30	2.14	7.5	
Flour, No. 2	Minneapolis	26.4	0.31	1.68	5.87	

(*Continued on next page*)

TABLE II—CONT'D

SAMPLE	VARIETY	SIZE (GM. OR ML.)	CD FOUND (μG)	CD PER 100 CALORIES*	CD PER 100 GM.	REMARKS
Grains (continued)						
Buckwheat, seed		20.9	1.50	—	7.2	
Bread, stone ground	Whole wheat	41.3	0.50	0.48	1.2	
Corn, fresh frozen		4.0	0.30	7.50	7.5	
Corn, dried, old	Local	4.0†	0	—	0	
Corn, fresh on cob	Local	40.6†	0	—	0	
Corn meal, special	N. H.	20.3	1.30	1.86	6.5	
Corn oil	Bottled	2.0	0.10	—	Trace§	
Oats, whole		23.1	1.88	2.03	8.1	
Oats, seed		25.7	0.63	—	2.4	
Oats, oatmeal		4.3	0.7	4.2	16.3	
Oats, precooked		9.8	1.25	3.18	12.7	
Wheatena		2.0	0.30	4.0	15.0	
Wheaties		13.4	0.20	—	Trace§	
Rye, whole		10.5	0	—	0	
Rye, whole flour cakes		26.4	0.05	—	Negl.‡	
Rice, precooked	American	15.8	0.60	1.10	3.8	Cf. Table VII
Animal Products.—						
Kidney						
Pork†			—	—	17–60	Cf. Table VI
Beef†			—	—	22–31	
Beef		10.0	6.7	—	67.0	Ref. 6
Liver						
Chicken	Local	4.7	0.20	—	Trace§	
Pork		10.0	0.2	—	0	Ref. 6
Pork	Local	10.0	0.1	—	10.0	
Beef		10.0	0.2	—	20.0	
Lamb chops		11.0	0.2	0.8	1.5	
Beef chuck		11.2	0.27	0.9	2.4	
Pork chops		10.2	0.25	0.7	2.5	
Gelatin, No. 1		1.5	0.3	5.0	20.0	
Gelatin, No. 2		7.8	0.2	—	Trace§	
Eggs, fresh	Local	12.0†	0.15	—	Trace§	
Vegetables and Fruits.—						
Apple, fresh		45.0	0.2	—	Trace§	
Apple cider		21.0	0.2	—	50/L.	
Potato, raw, No. 1		5.2	0	—	0	
Potato, raw, No. 2		57.7	0.05	—	Negl.‡	
Peas, tinned		25.0	0.2	—	0	Ref. 6
Peas, split green, dried		25.3	1.0	1.33	4.0	
Beans, kidney, red dried		26.7	1.39	2.0	5.2	
Beans, yellow eye, dried		25.9	0.34	0.22	1.2	
Beans, Navy, dried		25.2	0.38	0.54	1.5	
Beans, lima, fresh		9.6	0	—	0	
Cabbage, white		63.9	0.50	3.2	0.8	
Cabbage, red		91.8	0.63	3.5	0.7	
Kohlrabi leaves		35.7	0.88	—	2.4	Organic
Kale		33.3	1.25	—	3.8	Organic
Lettuce, iceberg		119.3	1.125	9.0	1.0	
Lettuce, fresh garden		31.1	0.53	15.4	1.7	Organic
Escarole		40.1	0.63	14.5	1.6	
Beet greens		103.0	3.75	32.7	3.6	
Swiss chard		59.3	1.75	11.6	2.9	Organic
Spinach, fresh		33.0	1.3	—	3.9	Ref. 6
Spinach, fresh		68.0	0.38	2.4	0.6	
Onions, yellow		57.8	0	—	0	
Chicory		19.9	0.75	34.5	3.8	
Tomato, fresh		128.0	0	—	0	

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TABLE II—CONT'D

SAMPLE	VARIETY	SIZE (GM. OR ML.)	CD FOUND (μG)	CD PER 100 CALORIES*	CD PER 100 GM.	REMARKS
Vegetables and Fruits (continued)						
Tomato paste		15.2	0.35	—	2.4	
Tomato juice		51.2	0.88	—	1.72	
Tomato juice		25.0	0.4	—	1.6	Ref. 6
Grapefruit juice, tinned		50.0	1.0	—	2.0	Ref. 6
Pineapple juice, tinned		50.4	0.18	—	Trace§	
Lemon juice, tinned, frozen		50.0	0	—	0	
Raisins, dried		13.6	0.1	—	Negl.‡	
Peanuts, fresh roasted		5.4	0.7	2.16	12.95	
Peas, frozen		17.2	0	—	0	
Peas, tinned		41.8	0.2	—	Negl.‡	
Cigarettes, filtered, whole		0.944	1.56	31.20 (pack)	165.2	

*Caloric values from McCance, R. A., and Widdowson, E. M.: The Chemical Composition of Foods, 1947, Chemical Pub. Co., Brooklyn, N. Y.

†Wet ash method.

‡Negl. = Negligible, or 0.05 μg or less found per sample.

§Trace, or 0.05 to 0.1 μg found per sample.

Analytical error ± 0.005 μg per sample except where indicated, where three series of analyses showed errors of 0.1 to 0.2 μg.

replaced fresh meat, the content could rise to more than 100 μg per day. On the other hand, intakes as low as 4 μg can be calculated without undue dietary restriction, using meat, potatoes, legumes, and eggs and avoiding seafoods and grains. Thus, the daily amounts ingested probably fluctuate widely and depend on the kind of food eaten. If these calculations are reasonably accurate it is probable that most of the cadmium ingested is absorbed and only a minor part is excreted in the feces.

Decker and her co-workers have examined accumulation of cadmium in the rat at levels of intake from 3 to 270 μg per day for one year.[17] The amount retained in kidney and liver was directly proportional to the intake, with kidney showing two to four times that in liver and reaching concentrations found in man. At a dosage of 3.1 μg per day, 0.51 per cent of the amount ingested was retained by liver and kidney at the end of a year.* This dose on a weight basis is roughly 25 to 60 times that estimated for man from this study.

Cadmium From Food Processing or Occurring Naturally.—A comparison of some fresh and processed foods revealed higher values in the latter: fresh and evaporated milk, fresh and tinned oysters, fresh, dried, and frozen corn and corn meal, fresh tomatoes, juice, and paste, refined sugar and its residue, molasses, fresh and dried beans. In these cases contamination may have occurred during the processing. It is also possible that the amounts found in baking powder, a

*The final concentrations in kidney were directly proportional to the intake, a straight-line function of dosage.

TABLE III. CADMIUM CONTENT OF WATER

SOURCE	CD μG/L. (PPB)	WATER PIPES AND REMARKS
Unpiped Water.—		
Spring, forest No. 1	0	
Spring, forest No. 2	0.06	
Brook, Brattleboro, Vt.	0.03	
Brook, W. Brattleboro, Vt.	0.37	Partly fed by 600 ft. polyethylene pipe (cf. Table IV)
Pond, artificial, fed by pipe	0.45	
Reservoir, Brattleboro, Vt.	0.08	
Reservoir, Hinsdale, N. H.	0.13	
Connecticut River, Brattleboro, Vt.	0.09	Low water
	0.09	High water
Sea water, S. Cape Cod		
Sea water, S. Cape Cod	0	Low tide
Sea salt	0	High tide
Condensed steam (Aqua-Stil)	0	
	0	
Piped Water, Public Places.—		
Inn, Hanover, N. H. (stale)	2.07	Galvanized
Hotel, old, New York	1.09	Probably galvanized
Roadside restaurant, Springfield, Vt.	0.65	Galvanized
Hotel, old, Boston	0.2	Galvanized
Hotel, new, Philadelphia	0.17	Copper
La Guardia Airport, New York	0.06	?
Cincinnati Airport	0	?
Hotel, old, St. Louis	0	?
Motel, new, Cape Cod (hot)	0	Copper
Motel, new, Cape Cod (cold)	0	Copper
Laboratory, Brattleboro Retreat.—		
Fresh, hot	0	Brass
Fresh, cold	0.06	Brass
Stale, hot	0	Brass
Stale, cold	0.64	Brass
Demineralized (Bantam)	0.03	(5 L. sample)
Piped Water, Private Houses.—		
Apartment, Cambridge, Mass. (city)	0	Galvanized
Princeton, Mass. (well)	0.7	Galvanized
Springfield, Mass. (city)	0	
Brattleboro, Vt.	0	
W. Brattleboro, Vt. (well)	0	Copper
Brattleboro, Vt. (well)	0.14	
Marlboro, Vt. (spring)	0.09	
Brattleboro, Vt. (reservoir)	0.03	
W. Brattleboro, Vt. (spring)	0.32	Galvanized
Hinsdale, N. H., fresh (reservoir)	0.10	Galvanized (reservoir 0.13 μg/L.)
Hinsdale, N. H., stale	0.25	
W. Brattleboro, Vt., cold, fresh (spring)	0	Galvanized and copper
W. Brattleboro, Vt., hot, fresh	0	Galvanized and copper
W. Brattleboro, Vt., cold, stale	1.10	Galvanized and copper
Spring, forest No. 1, at source, untouched 30 yrs.	0	No piping
Spring, forest No. 1, newly built and concreted		
Turbid	0.25	214 feet ¾ inch black polyethylene pipe and 3 feet copper
Filtered	0.25	
Spring, forest No. 1, 1 month later, clear	0.28	
Spring, forest No. 1, at source, overflow	0.17	Contains 3 feet black polyethylene pipe and black Scotch tape (Cf. Table VI)

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TABLE IV. UPTAKE OF CADMIUM AND COPPER FROM WATER PIPES* BY SOFT SPRING WATER (HARDNESS 18 PPM)

	pH	SURFACE AREA (CM.²)	DAYS EXPOSED	METAL DISSOLVED		REMARKS
				μG	μG/100 CM.²/DAY	
Cadmium.—						
¾ inch galvanized iron pipe, new	5.8	100.52	21	1.50	0.071	Both surfaces
Same (old)	5.8	84.96	21	0.11	0.006	Inner surface
¾ inch black polyethylene pipe, new	6.0	80.42	11	0.94	0.107	Both surfaces
Same	9.3	81.64	11	0.62	0.069	Both surfaces
¼ inch stainless steel tubing	6.0	73.48	21	0		
Rubber stopper, black, AHT No. 7	6.0	34.37	15	1.485	0.3	All surfaces
Copper.—						
¾ inch copper pipe, new	4.0	41.86	7	3105	1056.1	Both surfaces. pH adjusted with $MgSO_4$, $CaCO_3$, Na_2CO_3, H_2SO_4
	5.5	43.44	7	855	284.0	
	6.5	42.69	7	315	104.6	
	7.0	41.83	7	450	153.1	
	7.5	42.24	7	315	107.1	

*The lengths of pipe were immersed in 250 or 300 ml. of spring water and allowed to stand at room temperature, without stirring, for the time indicated. Diffuse corrosion was obvious in the cases of the galvanized and copper pipes.

bottled drink, and gelatin represent contaminants. On the other hand, six fresh sea foods and four fresh vegetable foods contained the metal in considerable concentrations, while other tinned, dried, and processed foods had little or none. Therefore, tinning or processing may introduce cadmium into foods only under certain special circumstances. It is possible, however, that some of these processed foods contained the metal before being processed.

The data indicate that cadmium occurs naturally in shellfish and Crustacea in large amounts,* the source being sea water. The chance of contamination of sea water by industrial wastes is remote, considering the locations of the catches (Maine, Cape Cod, Japan, Gulf of Mexico). It was present in one fresh fish but not always in tinned fish. All mammalian and avian kidneys analyzed concentrated it, while little or none occurred in muscle.[7,9]

Cadmium occurs naturally in the evergreen and apple twigs, bark, berries, and leaves tested. The chance of contamination of their soil is remote, for the

*At concentrations of 2,000 to 10,000 times that in the environment. Sea water is said to contain 0.03 to 0.075 ppb cadmium, according to H. W. Harvey as quoted by Mason.[26] Our inability to detect it in two samples of sea water or sea salt (Table III) suggests concentrations less than 0.05 ppb. Goldschmidt[43] quotes I. and W. Noddack as finding cadmium in nine marine animals in concentrations of 0.03 to 11 ppm dry matter, the higher values being in the range of our results. Concentration by marine animals of cadmium from the environment is considerably less, however, than that of vanadium by Ascidia (1 million times).[44]

TABLE V. CADMIUM IN KIDNEY AND LIVER

SAMPLE	ORGAN WEIGHT (GM.)	SAMPLE WEIGHT (GM.)	CADMIUM* (μG/GM. WET WEIGHT)	REMARKS
Kidney.—				
Beef	292.5	4.0	0.22	
Beef	———	5.0	0.31	
Beef	294.0	8.4	1.00	Organically raised
Beef	———	———	0.67	Ref. 6 (chem.)
Veal	———	5.0	0.04	Trace
Hog	95.1	8.39	0.60	
Hog	96.0	8.0	0.17	
Hog	———	5.0	0.15	
Hog	82.0†	10.09	0.29	
Hog	106.0	9.52	0.25	
Lamb	———	5.0	0.14	
Deer	73.9	8.81	11.7	
Deer	83.0	6.94	6.58	
Deer	62.0	5.03	2.38	
Deer	74.5	1.0	2.10	
Deer	89.0	0.4	2.37	
Deer	49.2	0.4	4.12	
Deer	58.5	0.5	3.70	
Deer (right)	63.9	0.95	4.02	
Deer (left)	59.0	0.83	3.60	
Red squirrel, male	1.60	0.4	7.97	Trapped
Red squirrel, female	1.70	0.17	17.35	Trapped, lactating
Gray squirrel, male	3.06	0.61	3.62	
Rabbit, wild, male	6.85	0.68	3.58	Trapped
Rat, Sprague-Dawley	———	———	0	1 year old (Ref. 24, chem.)
Starling	0.31	0.31	1.0	Shot, pistol
Robin, male	1.09	1.09	2.03	Killed, accident
Ruffed grouse, male	4.43	0.09	51.35	Killed, accident
Human, newborn, mean	———	———	0	Ref. 1 (spect.)
Human, 40 to 50 years, mean	———	———	39.0	Ref. 1 (spect.)
Human, <70 years, mean	———	———	23.7	Ref. 1 (spect.)
Human, all ages, mean	———	———	33.0	Ref. 1 (spect.)
Liver.—				
Chicken		4.71	Trace	
Hog		10.0	0	Ref. 6 (chem.)
Hog		10.0	0.1	
Beef		10.0	0.2	
Beef		31.7	0.16	Organically raised
Beef			0	Ref. 6 (chem.)
Deer†		1.6	0.56	
Deer†		4.0	0.35	
Deer		4.0	0.44	
Deer†		6.44	0.74	
Red squirrel, male	3.65	3.65	2.03	
Red squirrel, female	6.39	2.32	0.80	
Rabbit, wild, male	29.25	8.31	0.30	
Starling	3.06	3.06	0.57	
Robin, male	2.72	1.1	0.55	
Ruffed grouse, male	9.88	9.88	2.04	
Salmon, young	30.9	21.6	0.19	
Salmon, old	169.5	31.9	0.15	
Human, newborn			0	Ref. 1 (spect.)
Human, mean			2.44	Ref. 1 (spect.)
Aorta.—				
Rabbit, male	0.22	0.22	0	
Man, aged 82 years		10.5	0.09	
Human, mean			<0.6	Ref. 1 (spect.), usually absent

TABLE V—CONT'D

SAMPLE	ORGAN WEIGHT (GM.)	SAMPLE WEIGHT (GM.)	CADMIUM* (μG/GM. WET WEIGHT)	REMARKS
Heart.—				
Chicken	—	6.43	0	
Ruffed grouse, male	2.91	2.91	0.40	
Gray squirrel	3.00	1.20	0.54	
Human, mean			<0.6	Ref. 1 (spect.), usually absent

*The amounts of cadmium actually found in the sample were converted to micrograms per gram (ppm). When the amount found was equal to or less than the observed analytical error in recovery experiments, the concentration per 100 Gm. was considered negligible (Negl.). When the amount found was equal to or less than twice the observed error, the concentration was considered as a trace. The analytical error was usually 0.05 μg per sample, although by wet ashing it sometimes approached 0.2 μg.

†Wet ash method. All others by dry ash method.

Chem. = chemical method. Spect. = spectrographic method.

trees were growing in a forest in areas which had apparently never been cleared and in others which had not been farmed for over a hundred years. The apple trees had seeded themselves from an old orchard now virtually disappeared and overgrown by marketable timber. Presumably the cadmium was extracted from the subsoil.* It was not detected in a nearby spring.

Whether or not cadmium is natural or necessary in vegetable foods growing in topsoil is not clear from the data. Fourteen grains and grain products contained much, while five showed little or none. Of the legumes and leafy vegetables, amounts varied from none to fairly large. Fruits contained traces or none. The two root vegetables had none. Peanuts and tobacco had much. These inconsistent variations strongly suggest that a variable factor was interposed in the growing of these foods.

There are two logical explanations. Available cadmium varies from soil to soil. Data on this point are lacking. Or cadmium is introduced into some soils but not in others, probably by the use of fertilizers. The finding of high concentrations of cadmium in commercial phosphates is noteworthy. According to Eyles,[18] phosphate deposits in Jamaica which were probably laid down in Plio-Pleistocene time contain "surprisingly high concentrations" of cadmium as well as zinc, beryllium, and yttrium. This phosphate band is fossiliferous, made up almost entirely of small fish teeth. He states: "The above characteristics of the sedimentary band . . . suggest that it should be classified as a marine phosphorite, comparable in general character with, for example, the marine phosphorites of the Bone Valley formation in Florida.† . . " from which deposits come three

*Goldschmidt[43] suggests that cadmium, like zinc, may be concentrated in forest humus and litter because of its presence (up to 50 ppm) in coal, but gives no data.

†A sample of phosphate rock from Dunellon, Florida, in the British Museum was analyzed by Dr. P. A. Sabine at the request of Dr. Eyles. By the spectrographic method it contained less than 200 ppm cadmium and 1.8 ppm beryllium.[42]

TABLE VI. CADMIUM IN VEGETATION, ANIMAL FOODS AND BEDDING, FERTILIZERS, AND BUILDING MATERIAL

MATERIAL	CD(μG/GM.)	CD(μG/100 GM.)	REMARKS
Vegetation.—			
Hay, old*	0.51	50.5	Fertilized fields
Hay, fresh No. 1*	0.23	22.5	Fertilized field
Hay, fresh No. 2*	0	0	Unfertilized field
Wild bird seed mixture*	0.05	Negl.	
Sumac berries	0.03	3.0	
Hemlock, Canadian:			
Needles	0.34	33.77	Forest
Twigs	0.01	Negl.	
Bark	0.26	26.0	
Apple, No. 1 wild, 6 inch diam.			
Leaves	0.14	14.0	Forest, self-seeded
Twigs	0.22	22.0	
Apple, No. 2, domestic, 14 inch diam.			
Leaves	0.03	2.8	Not sprayed for 30 years
Twigs	0.10	10.0	
Apple, No. 3, wild, 3 inch diam.			
Leaves	0.06	5.9	Forest, self-seeded
Fruit	0.03	2.6	
Apple, No. 4, wild, 4 inch diam.			
Leaves,	0.21	21.0	Forest, self-seeded
Twigs	0.19	19.0	
Fruit, green	0	0	
Pine, white, needles	0.14	14.0	Forest
Spruce, white, needles	0.15	15.0	Forest
Juniper, wild, needles	0.29	29.0	Abandoned field
Twigs	0.30	30.0	
Bark	0.43	43.0	
Berries	0.10	9.8	
Seaweed	0.02	1.5	
*Animal Foods, Prepared.**—			
Chow, laboratory	0.09	9.0	
Dog food, dry	0.09	8.6	
Beet pulp	0.58	57.5	
Poultry wheat	0.02	2.0	
Calf food	0.04	Negl.	
Animal Bedding.—			
Sawdust, soft wood	0.25	25.0	Local sawmill
Shavings, soft wood	0.05	4.96	Planing mill, N. H.
Peat moss, sphagnum	0.04	3.75	
Paper, shredded, excelsior	0 01	1.0	
Cellophane excelsior, white	0	0	
Cellophane excelsior, red	0.08	8.0	
Newsprint, raw	0.06	6.0	
Paper towels	0.001	Negl.	
Polyurethane foam	0	0	
Fertilizers.—			
Commercial, 7-7-7	1.41	141.0	
Phosphate, 0-20-0, Florida	1.80	179.0	
Commercial, 0-15-30	2.05	205.0	
20% Super-phosphate, Florida	2.30	230.0	
Phosphate rock, Tennessee	0.13	12.5	
Cow manure, fresh	0.25	25.0	From hay No. 1 and beet pulp

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TABLE VI—CONT'D

MATERIAL	CD(μG/GM.)	CD(μG/100 GM.)	REMARKS
*Building Materials.**—			
Cement, old	0	0	From cow barn
Whitewash, old	0	0	From cow barn
Sheet rock, board	0	0	
Sheet rock plaster	0.13	12.5	
Wallboard, paper	0.27	27.0	
Building paper, tar	0.05	Trace	
Building paper, plain	0.09	9.1	
Plastic wood	0.08	7.5	
Miracle wood	0.88	87.5	
Shellac	0.04	4.38	
Varnish, floor	0.04	4.38	
"Fabulon" plastic	0	0	
"Krylon" plastic	0	0	
Miscellaneous.—			
Rock salt, crude (roads)	0		
Calcium chloride, crude (roads)	0		
Filter-cel (Celite)	±5.0		Large amount present
Pipe, polyethylene, black, ¾ inch	0.30		Cf. Table IV
Scotch tape, black	1.30		
Scotch tape, glass fiber	0.89		

*Wet ash method. All other by dry ash method.

The amounts of cadmium actually found in the sample were converted to micrograms per gram (ppm). When the amount found was equal to or less than the observed analytical error in recovery experiments, the concentration per 100 Gm. was considered negligible (Negl.). When the amount found was equal to or less than twice the observed error, the concentration was considered as a trace. The analytical error was usually 0.05 μg per sample, although by wet ashing it sometimes approached 0.2 μg.

quarters of the commercial phosphate fertilizers used in this country.[19] The inference is clear that the cadmium in rock phosphates came from the sea via fish teeth.* Seed rye is seldom fertilized with phosphate[19] as it will grow in poor soils; local corn is usually manured, while vegetables may or may not have phosphates applied. "Organic" growers use phosphates. Therefore, some of the cadmium found in vegetable foods of cattle and man may come from phosphate fertilizers rather than from topsoil. The use of commercial phosphates for growing wheat, peanuts, tobacco, legumes, and grasses (all of which contain much cadmium) is now widespread.[19] Phosphates form strong complexes with zinc and cadmium. This hypothesis, which requires further proof, is consistent with the data.

Human Sources.—The major immediate sources of cadmium in adult American man on a normal western diet appear to be in sea foods, kidneys, and grains.† Cigarettes may be a potential contributor when the boiling point of cadmium

*Zinc-bearing phosphorites from Oceanic islands contain about 100 ppm Cd, which could be derived only from marine organisms which concentrated it from sea water, according to Goldschmidt.[43]

†A few of these foods have been reported to contain high levels of zinc[20] but the association of high cadmium and high zinc is by no means regular. Zinc of 20 to more than 50 ppm has been found in oysters, gelatin, whole wheat flour, oatmeal, cocoa, molasses, tea, mussels, which are also high in cadmium. On the other hand, zinc levels of less than 8 ppm were found in most sea fish, polished rice, green vegetables, white flour, most of which contained appreciable amounts of cadmium. Some others with little or no cadmium contained much zinc: eggs, peas, beans, onions. Most fruits and vegetables were low in both metals.

TABLE VII. CADMIUM IN JAPANESE FOODS*

SAMPLE	ORIGIN	SIZE OF SAMPLE (GM.)	CD FOUND (μG)	CD (μG/100 GM.)	REMARKS
Rice.—					
Polished, common	Yokote Akita	7.30	1.0	13.7	
Polished, common	Odate, Akita	13.71	1.45	10.6	
Polished, common	Kurashiki, Okayama	8.00	1.0	12.5	
Polished, common	204 samples	9.01	0.7	7.7	From all areas
Bran	Okayama	5.10	0.2	3.9	
Unpolished, special	Kojyo, Okayama	8.00	0.7	8.75	
Polished, special	Kojyo, Okayama	9.77	0.1	(1.0)	Trace
Wheat.—					
Whole	Kojyo, Okayama	15.89	1.15	7.2	
Flour	Okayama	2.49	0.4	16.0	
Whole	Matsubara, Takahashi	13.0	0.7	5.4	
Sake, exported	Shizuoka	40 ml.	0.6	7.5	500 ml.
Crabmeat, tinned	Exported	20	2.45	12.25	
Tea.—					
Coarse, green		3.34	0.88	0.52	2 Gm.
Fine, green		11.9	0.91	0.16	2 Gm.
Refined green		12.0	0.55	0.09	2 Gm.

*Samples furnished by Professor Jun Kobayashi.

(767° C.) or its compounds is exceeded in the burning of tobacco. Most foods high in this element, other than grains, are irregularly used. Evaporated milk may be a source for infants.

In the Japanese, the very high concentrations of renal and hepatic cadmium may be partly accounted for by the high concentrations found in rice and flour and partly by those in seafoods. While no survey of other Japanese foods has been made, 400 Gm. of mixed rices would provide 31 μg of cadmium and of some rices 50 μg, while 100 Gm. of lobster or crabmeat washed down by sake would provide 20 μg more. Whether high concentrations are natural to Japanese soil or cadmium has been added in phosphate fertilizers is not known. Livers and intestines of an edible river fish, Ayu, are said to have cadmium, especially in northeastern areas.[21]

Animal Sources.—Cadmium in the kidneys and livers of wild deer apparently does not come from industrial contaminants, rock salt, and calcium chloride on roads, or to any appreciable extent from water. The major sources appear to be in foliage and in evergreen leaves and twigs on which the animals browse during the winter. In the kidneys and livers of wild birds, squirrels, and rabbits, similar sources are probable, especially buds, seeds, and berries. While the rabbit, squirrels, and grouse were local, the starling was not, being a member of a flock migrating southward. Analyses on larger series and varieties of wild animals and birds are desirable.*

*Tipton found 13.7, 11.5, and 2.8 ppm cadmium in the kidneys of 3 female Tennessee deer, and 5.5 ppm in a male.

Sources in the kidneys and livers of domestic herbivorous animals are partly apparent. Levels were lower than in deer; the age of beef and hogs at time of slaughter is usually 2 years or less, while that of the deer was 2 to more than 6 years. Lamb and veal showed little. Hay, grains, and prepared foods contained enough cadmium to accumulate, especially when the hay came from fields fertilized with commercial phosphate, where it contained 1 or 2 ppm.

Environmental Cadmium.—The difficulty of providing a "cadmium-free" environment for laboratory animals is indicated in Table VI. Some building materials, pine wood, varnishes, and most paints are contaminated, while others are not. Animal quarters need to be free of all galvanized articles and wood protected by plastic coating. Provision of an efficient cadmium-free bedding is a serious problem.

Cadmium in Water.—Certain slightly acid waters low in calcium and magnesium will attack the pipes through which they run and take up appreciable quantities of copper, lead, zinc, or cadmium. Hard alkaline waters tend to deposit insoluble salts in pipes, protecting them from corrosion. Acute cadmium poisoning has been caused by contact of citrous fluids with cadmium-coated containers and ice trays, for example.[22] Waters naturally soft tend to be acid. Galvanized iron pipes contain cadmium as a natural contaminant of zinc, at concentrations up to 1 per cent or more.[23]

That natural waters can take up metals from metal water pipes is shown in Table IV and is well known. The spring water used (which has approximately 3 ppm sodium), standing 24 hours in a ¾ inch copper pipe 10 M. long at pH 5.5 could conceivably dissolve copper to the extent of 60 mg. per liter and at pH 5.8 dissolve cadmium up to 6 μg per liter from a galvanized pipe and up to 4 μg per liter from a black polyethylene pipe. The concentrations of cadmium found in several tap waters, however, were not large. Flushing out the water system often lowered the content to an amount undetectable. These analyses indicate that cadmium is not always a constant contaminant of natural waters in this area, although it may be present sometimes in appreciable quantities. They also show that soft water remaining overnight in galvanized or black polyethylene pipes can take up 0.15 to 1.1 μg cadmium per liter. The amount contributed to man's total pool by 2 L. of water per day is small, no more than 1 or 2 μg at the most.*

Cadmium and Age.—The curve of renal cadmium with age is intriguing. A lessening of concentration with age coupled with a wide scatter of values at all ages† suggests three possibilities: (1) The intake of cadmium declines with age

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*Cadmium was detected in only 3 of 51 samples of river water analyzed by the National Water Quality Network, from the Arkansas (8 to 70 μg per liter), the Delaware (20 μg per liter), and the lower Mississippi (7 μg per liter).[41] We have found it in old snow exposed to motor vehicle exhausts at concentrations up to 1.0 ppm but not in new-fallen snow. The amounts in three-fourths of urban-air samples measured by the National Air Sampling Network were between 0.002 and 0.02 μg per cubic meter and none was above 0.2 μg.

†Extreme variations of cadmium in kidneys with age were as follows: (ppm ash) newborn, 0; first decade 0 to 1,750; second decade 0 to 4,000; third decade 570 to 3,550; fourth decade 640 to 8,000; fifth decade 1,650 to 6,600; sixth decade 1,500 to 6,800; seventh decade 900 to 6,100; eighth decade 1,100 to 4,100; ninth decade 1,500.

and the urinary loss continues. (2) Urinary losses increase in older persons. (3) Persons with high concentrations do not live as long as those with low concentrations. Enough facts to answer these questions are not known. Lowered food intake is not necessarily associated with a lessened intake of cadmium unless certain foods are eliminated. Perry and Perry[16] found higher urinary concentrations in two older men than in younger adults. Most of the values in kidneys were taken from persons having accidental or sudden deaths; therefore, the third possibility cannot be answered one way or the other. The cadmium-protein complex in horse kidney appears to be very stable[24] and, although its human counterpart has not been investigated, it must represent a strong insoluble chelate. Cadmium given in a single oral dose to rats remains in the kidney for two weeks[25] and in man no way effectively to lower renal or increase urinary concentrations is known.[16]

Biologic Activity.—Cadmium ranks fifty-fourth of 90 stable elements in order of abundance in the universe, with a ratio to zinc of 1:544 and sixty-fifth of 80 elements in order of abundance in the earth's crust, with a ratio to zinc of 1:325. In sea water it ranks thirty-sixth of 40 minor elements with a ratio to zinc of 1:469.[26] In the tissues of adult American man it ranks twenty-first of 46 elements in abundance with a ratio to zinc of 1:73, and in his kidneys ninth of 46 elements with a ratio of 2:3.[7] Cadmium thus appears to be a unique metal in being concentrated in kidney against such a gradient,* ranking third, after iron, of the minor elements.

Is cadmium an essential metal?

Although little is known of its biologic effects in small doses, available data indicate that when any action on living organisms, organ functions, and enzyme systems is exerted, that action is inhibitory.[8] For example, injected into rabbits, this element was reported to induce hyperglycemia and decrease the oxidation of phenol and to retard the formation of glycogen in the rat diaphragm.[14] It is lethal to various aquatic life at low concentrations[27]: to sticklebacks at 0.2 ppm, to goldfish at 0.0165 ppm, to *Daphnia magna* at 0.0026 ppm, to a flatworm, *Polycelis nigra*, at 2.7 ppm. These toxic levels are in the same range as those of copper salts. At 1 ppm[28] and 10 ppm,[29] cadmium salts are toxic to the perfused frog heart and in larger doses to the perfused turtle, frog, and dog hearts.[30]

At concentrations of 0.56 ppm cadmium has been shown to interfere with oxidative phosphorylation in rat liver mitochondria[31]; this concentration is considerably less than that found in adult human kidney (32 ppm) and liver (2.44 ppm) and approximates that in beef. It is a strong inhibitor at 11 ppm of renal l-aromatic amino acid decarboxylase, using DOPA as a subtrate,[32] and 4 other enzymes.[8] The only documented instance found of apparent specific activation of an enzyme system by cadmium was that of histidase; other divalent ions were less active[33]; in the hands of others cadmium inhibited this enzyme at 0.0001 M concentration, according to a summary report,[34] and the matter remains unsettled.

*Cadmium has not usually been detected in plant and animal tissues prior to the last decade probably because of the prevalent use of high temperatures for ashing, which boil it off. In most geochemical surveys of the biosphere cadmium is not listed.[26,43,44] Tipton[1] was the first to call attention to its presence in man.

Urease is extremely susceptible to inhibition by cadmium ions.[34] In the older literature are many references to inhibition by cadmium of enzymes such as rennin, amylase,[35] papain,[36] catalases and peroxidases,[37] invertase, reductase, carboxylase,[38] malt diastase,[39] at concentrations of 0.001 to 0.000001 M. For arginase, nonspecific activation has been observed.[34]

Cadmium appears to be one common metal which the mammalian body handles poorly. Renal accumulation with age in man, accumulation as a straight-line function of dosage,[17] and retention of single doses in rats,[25] the stability of the renal protein chelate in horses,[24] and resistance to chelating agents in man (zinc being readily mobilized and excreted by these agents[16,40]) suggest that cadmium behaves differently from other common ubiquitous metals in mammals, such as lead, tin, bismuth, silver, nickel, and gold. Given by mouth, the essential trace metals are relatively nontoxic in comparatively large doses and are either not absorbed or are readily excreted; in the experience of one of us (H.A.S.) doses approximating the total bodily pool of cobalt, manganese, and molybdenum (as well as vanadium) have been fed to human beings for many weeks without observable toxic effects, while doses of zinc and copper are limited by their ability to cause local irritation. From a review of all the data available, one can conclude *at present* that if cadmium is an essential trace metal, its primary action is that of inhibition. If so, it becomes of more than usual biologic interest, especially in man where its concentrations are so high.

In a previous discussion[8] it was postulated that any element not present in plants was not essential for man; likewise, any element found in man but not in plants was an environmental contaminant. At that time data here presented were not known and cadmium was included as a probable environmental contaminant. From these analyses it would appear that cadmium can occur naturally and be concentrated from subsoil in the leaves of certain trees and by Mollusca and Crustacea from sea water. Occurrence in most vegetable foods is sporadic and unpredictable. The data suggest, however, that the high concentrations found in man in certain areas of the world but not in others may be partly the result of contamination of foods by processing or by phosphate fertilizers.

SUMMARY AND CONCLUSIONS

Cadmium appears to accumulate in the human kidney with age up to the sixth decade, at which time its concentration declines. It is virtually absent in the newborn. Average mean peak concentration in Americans was about 40 mg. per kilogram wet weight by spectrographic analyses. Concentrations in Japanese kidneys were about twice as great.

In order to discover where this cadmium came from, chemical analyses of more than 150 foods and waters were made. The major sources for Americans appeared to be in seafoods and grain products. Water from galvanized pipes contributed little to the total daily intake. Daily exposure to ingested cadmium was assumed to be somewhat sporadic, i.e., it was present only in certain special foods, which, with the exception of flour, are not eaten daily. Evidence is presented from the data that the intake of cadmium in man can vary from 4 to 60

μg per day, depending on the foods chosen. A rough estimate of the rate of accumulation in the body and known urinary excretion rates suggests that most if not all of the cadmium ingested is absorbed. High levels of cadmium in Japanese rice (and seafood) probably accounted for the higher renal concentrations in Japanese than in Americans. Estimated daily intakes were about double those of Americans and were probably relatively constant.

In order to discover whether cadmium in foods occurs naturally or is an environmental contaminant, analyses were made on over 60 natural and artificial products and on 43 kidneys and livers of wild deer and other animals. The data offer evidence for both hypotheses in specific cases: (1) Cadmium occurs naturally in high concentrations in all salt water Mollusca and Crustacea tested, the ultimate source obviously being sea water. It was found in the kidneys and livers of wild deer, squirrel, a rabbit, and three birds, and in twigs, bark, and leaves of forest evergreens and apple trees, presumptive sources for wild animals. Contamination of sea water and forest soil was unlikely. (2) Cadmium occurred with no constancy or regularity in vegetable foods. All grain and grain products but three showed high concentrations. Fertilizers containing rock phosphates had relatively large amounts of cadmium. Foods usually fertilized with phosphates contained, in general, the higher levels of this metal, and the converse appeared to hold. The presumptive evidence is that rock phosphates are sources in many foods.

Processing and canning apparently accounted for some of the cadmium in foods, but these influences were inconstant and the foods may have originally contained it. Cadmium in foods of domestic animals probably accounted for its presence in their kidneys and livers, where concentrations were much lower than in those of wild animals.

Whether or not cadmium is an essential trace metal cannot be answered at present. Its biologic actions are virtually always inhibitory. The high concentrations in human kidneys suggest exposures greater than have been found in many ordinary foods.

We are indebted to Dr. Isabel H. Tipton for use of the voluminous raw data collected by her colleagues and to Miss Shalini N. Valanju, M.Sc., for some of the analyses.

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VARIATION IN THE CONCENTRATION OF CADMIUM IN HUMAN KIDNEY AS A FUNCTION OF AGE AND GEOGRAPHIC ORIGIN

H. Mitchell Perry, Jr., M.D.,*
Isabel H. Tipton, Ph.D.,**
Henry A. Schroeder, M.D.,***
Robert L. Steiner, M.S.,****
and Mary Jane Cook, M.S.*****

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo.; Department of Physics, University of Tennessee, Knoxville, Tenn.; and Health Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.

(Received for publication Dec. 30, 1960)

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WHILE analyzing human organs for trace metals, one of us (Tipton) observed surprisingly large amounts of cadmium in the kidney.[1] This unexpected observation prompted a search for factors correlated with the concentration of renal cadmium. In order to explore the effect of age, kidneys of children from St. Louis were compared with kidneys of adults from St. Louis. In order to explore the effect of geographic origin, kidneys of adults from various parts of the world were compared with kidneys of adults from St. Louis.

Liver was the only other organ which consistently contained measurable concentrations of cadmium by the spectrographic technique used.[1] Therefore both hepatic and renal concentrations were studied. Cadmium lies directly below zinc in the periodic table and the two metals are chemically similar; moreover, cadmium is quite different from any other metal commonly found in the human body. The concentration of cadmium, which has no known biologic function, was therefore compared with that of zinc, which is essential to man. Accordingly, both renal and hepatic concentrations of both cadmium and zinc have been presented.

The ideal source of tissues for analysis would seem to be healthy subjects who died suddenly and traumatically. Even in the United States, however, children meeting this criterion were difficult to find; while in places like the non-industrialized areas of Africa, no such subjects were available. It was therefore necessary to use hospitalized patients who had died of various illnesses. Any disease known to produce hepatic or renal abnormalities was excluded; moreover, only grossly normal tissues were assayed.

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*Established Investigator of the American Heart Association, Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

**Department of Physics, The University of Tennessee, Knoxville, Tenn.

***Formerly with the Hypertension Division at Washington University School of Medicine. Now with the Department of Physiology, Dartmouth Medical School, Hanover, N.H.

****Formerly with the Department of Physics at The University of Tennessee. Now with the Research Laboratories of the Aluminum Company of America, New Kensington, Pa.

*****Health Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.

Since freezing seems to be the ideal method of preserving tissues, samples collected in the United States were frozen. Unfixed human tissue cannot be imported; therefore formalin was added to the foreign samples. The addition of any substance to a tissue raised the possibility of contamination, and the immersion of a tissue in any liquid raised the possibility of eluting trace constituents. Falsely high analytical values from contamination were excluded by demonstrating the purity of the preservative. Losses from elution were excluded by analysis of the preserving fluid together with each tissue. Moreover, comparisons were limited to tissues that had been similarly handled. Thus assays were performed on two aliquots of each tissue from the American adults. Frozen aliquots were compared with frozen tissues from American children, and formalin-preserved aliquots were compared with formalin-preserved tissues from foreign adults.

MATERIAL

The kidneys and livers of 157 subjects were analyzed for cadmium and zinc. Organs with gross pathologic abnormalities were excluded. No subject was known to have had any industrial or other unusual exposure to metal. The subjects belonged to three categories: American adults, American children, and foreign adults.* The American children were divided into three age groups and the foreign adults were divided into eight national groups.

The 24 American adults ranged in age from 46 to 77 years. The 38 American children were 12 years of age or less, and 7 were stillborn. All American subjects died in St. Louis and the autopsies were performed by the members of the Department of Pathology of the Washington University School of Medicine. Table I presents information about sex, age, race, and cause of death.

The 95 foreign adults came from ten cities in eight different political units of Europe, Africa, and Asia. Their ages ranged from 20 to 79 years. The cultural pattern of the 9 Swiss subjects resembled that of the Americans. The subjects from Ruanda-Urundi came from primitive farming communities with little exposure to industrial civilization; in addition their diets were unusually poor in protein. The Nigerian subjects died in the city of Lagos, but many had spent time in the interior. The Asiatic subjects belonged to relatively nonindustrialized cultures; all except the Indians came from coastal areas and may have consumed considerable seafood. Autopsies were performed within 12 hours of death by the pathologists whose help is subsequently acknowledged.

COLLECTION AND PREPARATION OF TISSUES

At the time of autopsy, an aliquot of renal tissue from each American subject, both adult and child, was sealed in an individual polyethylene bag and immediately quick frozen. Hepatic tissue was sealed in a separate bag and frozen. The samples remained frozen until just before drying and ashing at the Oak

*The term "American" designates subjects from the United States and the term "foreign" subjects from the Eastern Hemisphere.

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TABLE I. DESCRIPTION OF SUBJECTS

GROUP	NO. OF SUBJECTS	PERSONAL DATA			CAUSES OF DEATH						PER CENT ASH*	
		NO. OF MALES	MEAN AGE (YEARS)	RACE	INFECTIOUS	NEOPLASTIC	CARDIOVASCULAR	CONGENITAL ANOMALY	TRAUMATIC	MISCELLANEOUS	KIDNEY	LIVER
American Children.—												
0–45 days	17	11	.003	10 Caucasoid†	1			8	1	7	1.16	1.17
45–450 days	10	5	.55	7 Caucasoid†	3	1		5		1	1.06	1.11
450–4500 days	11	8	4.5	8 Caucasoid†	2	4		3	1	1	1.19	1.41
American Adults.—												
Frozen tissue	24	14	62	23 Caucasoid†		3	16			5	1.02	1.23
Formalin tissue	24										4.0	4.1
Foreign Adults.—												
Ruanda-Urundi	11	7	32	Negroid	3		2		4	2	5.2	5.0
Nigeria	13	8	40	Negroid	6	1	1		3	2	5.3	5.3
Switzerland	9	5	54	Caucasoid		4	4		1		4.4	4.7
India	16	14	38	Caucasoid	1		1		12	2	5.3	5.3
Formosa	9	9	40	Mongoloid	1	5	1		2		4.2	3.9
Thailand	10	5	32	Mongoloid	1	3	1		2	3	4.6	4.5
Hong Kong	10	9	51	Mongoloid	4		4		1	1	5.1	4.9
Japan	17	12	42	Mongoloid	2	2	6		6	1	4.4	4.5

The autopsies from Ruanda-Urundi were performed in Usumbura, those from Nigeria in Lagos, those from Switzerland in Bern, 8 of those from India in Bombay and 8 in New Delhi, those from Formosa in Taipei, those from Thailand in Bangkok, and 8 of those from Japan in Kyoto and 9 in Tokyo. The miscellaneous causes of death included asthma, emphysema, diabetes mellitus, myasthenia gravis, beri beri, ectopic pregnancy, barbiturate poisoning, fibrinous pneumonitis, disseminated lupus erythematosus, and "unknown."

*Per cent ash of the frozen (American) tissue is the mean percentage of the *wet* weight of the tissue which remained after ashing. Per cent ash of the formalin-preserved (adult) tissue is the mean percentage of the *dry* weight of the tissue which remained as ash.

†The other subjects in these four groups were Negroid.

Ridge National Laboratory when they were thawed, trimmed of fat and connective tissue, and cut into cubes approximately 1 cm. on a side. Each sample was then placed in a tared silica dish, weighed, and dried at 110° C. for 24 to 48 hours. Thereafter the dried sample was reweighed, ashed at 450° C. for 24 hours or longer if necessary, and reweighed again. The gray ash was then transferred to a 15 ml. polyethylene bottle where it was thoroughly ground and mixed by shaking with platinum beads in a pipette shaker for 30 minutes. After the beads had been removed, the ash remained in the bottle until analysis. Table I indicates the percentages of kidney and liver which were ash.

At the time of autopsy, an aliquot of renal tissue from each adult subject, both American and foreign, was trimmed of fat and connective tissue, placed in an individual polyethylene bottle, and preserved in an approximately equal volume of formalin. Similar amounts of hepatic tissue and preservative were placed in a separate bottle. Each sample and all of the formalin in which it had been preserved were removed from the bottle at Oak Ridge and dried at 110° C. for 24 to 48 hours in a tared silica dish. Thereafter the dried formalin-preserved sample was handled in the same manner as the dried frozen tissue.

Except for stainless steel scalpels, nothing but polyethylene, fused silica, and platinum touched frozen samples from the time of collection until they were mixed with graphite and internal standard just prior to analysis. Before use, all polyethylene bottles and silica dishes were washed in five parts of concentrated nitric acid and one part of concentrated sulfuric acid; thereafter they were rinsed in metal-free water, soaked for 24 hours in a solution of ethylenediaminetetraacetate at pH 11, and rerinsed five times in metal-free water. All water used in the procedure was distilled in glass and then passed slowly through an ion exchange resin before being stored in polyethylene bottles.

Except for the addition of formalin, the other samples were similarly handled. Metal-free formalin was specially prepared by E. I. du Pont de Nemours & Co. Aliquots, equal to at least thrice the volume added to any one tissue, were stored for several months in bottles of the type used for tissue collection and then analyzed for zinc and cadmium. For the analysis 100 mg. of spectroscopically pure sodium chloride was added to the formalin and the mixture was dried, ashed in a muffle furnace at 450°C. for 24 hours, and then handled like tissue ash. No cadmium or zinc was detected in the formalin.

SPECTROGRAPHIC PROCEDURE

The spectrographic analyses were performed at the University of Tennessee. Five milligrams of ash from each tissue was mixed with an equal amount of spectroscopically pure graphite to which indium oxide had been added as an internal standard. Each sample was then placed in a crater 5 mm. deep and 1/16 inch in diameter in a *spec. pure* 1/8 inch graphite electrode. The electrode was made the cathode in a 10 ampere direct current arc and burned for 10 seconds, after which all the cadmium and zinc were gone from the sample. The region of the arc 1 mm. above the cathode, "the cathode layer," was focused on the collimator of a Bausch & Lomb Littrow spectrograph with a slit width of 20μ. The spectrum

from 2,400 to 3,400 Å was photographed on Eastman SA-2 plates which were developed for 3 minutes in D-19 developer, fixed for 16 minutes in F-5 fixer, and washed for 30 minutes in running water. The intensities of the 3,345.0 Å zinc, 3,261.1 Å cadmium, and 3,039.4 Å indium lines were read on a densitometer which had been modified to read intensities directly.

Working curves were made by burning, under identical conditions, standard samples which had been prepared by adding known quantities of trace elements, including cadmium and zinc, to a synthetic tissue ash. The synthetic ash was composed of 56.2 per cent KPO_3, 38.2 per cent NaCl, 2.5 per cent $CaCO_3$, 1.7 per cent MgO, and 1.4 per cent $FeCl_3$. Spectra of standards were included on every plate of unknowns.

To estimate the precision of the spectrographic method and the recovery of cadmium and zinc at the concentrations in which they occur in tissues, samples were prepared by adding known quantities of the two metals, both alone and in combination with known quantities of other trace elements, to a well-mixed composite of several different tissue ashes. The observed cadmium and zinc concentrations for 32 analyses of such samples during four months are shown in Table II. The minimum measurable amount of cadmium approximated 50 γ per gram of tissue ash. No check of the spectrographic method was made by colorimetry or wet chemistry. A complete description of the method has been published.[2]

TABLE II. RECOVERY AND REPRODUCIBILITY OF METHOD (32 ASSAYS)

	COMPOSITE TISSUE ASH	COMPOSITE ASH + 100 γ Cd/GM.	RECOVERY	COMPOSITE ASH + 1,000 Cd/GM. AND 2,000 γ Zn/GM.	RECOVERY
Cadmium	159	257	98	1,150	991
Standard error	±4	±7		±40	
Zinc	5,000			7,400	2,400
Standard error	±160			±240	

All tabulated values are average concentrations of metals found, or their standard errors, expressed as γ per gram of ash. The amount of metal recovered is obtained by subtracting the experimentally determined value for the composite tissue ash from the experimentally determined value for the composite ash plus added metal.

RESULTS

The Effect of Age (Frozen Tissues From American Subjects).—Each of the 24 adults from St. Louis had measurable concentrations of both cadmium and zinc in the frozen aliquots of both liver and kidney. The concentrations of cadmium in kidney ranged from 560 to 4,300 γ per gram of ash, and the median concentration was 2,075 γ. The median concentration of renal zinc was 3,700 γ per gram of ash. The median concentration of cadmium in the liver was a sixth as much as in the kidney, while the median concentration of hepatic zinc

exceeded that of renal zinc. The first part of Table III includes the medians and ranges of renal and hepatic cadmium and zinc for the American subjects, and the second part includes the means and their standard errors.

Among the adults, no apparent relationship was observed between sex and renal or hepatic cadmium or zinc; moreover, figures for the single adult Negroid subject approximated the average of the entire group in all four parameters. Specifically, the 10 females had a median concentration of 1,950 γ and a mean concentration of 2,010 γ cadmium per gram of renal ash; the Negroid subject had 2,000 γ of cadmium per gram of renal ash.

TABLE III. CADMIUM AND ZINC CONTENT OF 62 AMERICAN KIDNEYS AND LIVERS (FROZEN TISSUE)

AGE GROUPS	NO. OF SUBJECTS	KIDNEY		LIVER	
		CADMIUM	ZINC	CADMIUM	ZINC
Medians and Ranges.—					
0–45 days	17	0 (0–0)	3,000 (1,450–8,200)	0 (0–0)	9,000 (3,600–21,000)
45–450 days	10	0 (0–780)	2,950 (1,750–5,500)	0 (0–0)	3,950 (1,950–5,100)
450–4,500 days	11	360 (0–2,200)	3,700 (1,100–4,900)	50 (0–2,000)	3,700 (1,400–8,400)
>45 years	24	2,075 (560–4,300)	3,700 (2,150–6,000)	360 (50–1,200)	5,400 (2,450–13,500)
Means and Their Standard Errors.—					
0–45 days	17	0	3,850 ± 490	0	9,800 ± 1,235
45–450 days	10	86 ± 74	3,150 ± 318	0	3,875 ± 399
450–4,500 days	11	631 ± 192	3,465 ± 292	178 ± 76	4,760 ± 694
>45 years	24	2,150 ± 170	3,810 ± 194	335 ± 62	5,735 ± 498

The metal concentrations are expressed as γ per gram of ash.

None of 17 infants less than 45 days old, and only 2 of 10 infants between 45 and 450 days old had detectable renal or hepatic cadmium. In contrast, renal cadmium was found in 9, and hepatic cadmium in 6, of 11 older children; moreover, each of 4 children 6 or more years old had cadmium in both organs. Renal zinc varied less with age, as did hepatic zinc after the first few days of life, when nearly twice the adult concentration was present (Table III).

The Effect of Geographic Origin (Formalin-Preserved Tissues From Adults).— The metal concentrations in the formalin-preserved and frozen aliquots of the tissues from American adults were very similar. The figure presents individual concentrations of cadmium and zinc as cumulative frequency graphs for the formalin-preserved kidneys of the adult Americans and the eight foreign national groups. The graphs define ranges of values for both metals and cite median values. Table IV indicates the means and their standard errors for renal and hepatic cadmium and zinc in the formalin-preserved tissues. The same table includes the ratios of renal cadmium to both renal zinc and hepatic cadmium.

The total range of cadmium concentrations in the kidney extended from 150

to 17,000 γ per gram of ash for the 95 foreign adults; thus there was more than a hundred fold difference between the maximum and minimum values. Within the individual national groups, however, variation was less; in fact, for each of them a factor of 10 encompassed 90 per cent of the concentrations. The median renal cadmium concentrations of the national groups ranged from 720 to 5,300 γ per gram of ash. The large intergroup differences suggested several distinct populations; for example, exclusion of the single relatively high concentration among the subjects from Ruanda-Urundi eliminated all overlap between that group and the groups from Japan and Hong Kong. In general the foreign Negroid subjects tended to have less renal cadmium than the American Caucasoid, while the foreign Caucasoid subjects had similar amounts and the foreign Mongoloid had more (Fig. 1).

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TABLE IV. MEAN CADMIUM AND ZINC CONTENT OF 119 ADULT KIDNEYS AND LIVERS (FORMALIN-PRESERVED TISSUE)

COUNTRY OF DEMISE	NO. OF SUBJECTS	KIDNEY		LIVER		RATIOS	
		CADMIUM	ZINC	CADMIUM	ZINC	RENAL Cd / RENAL Zn	RENAL Cd / HEPATIC Cd
Ruanda-Urundi	11	710± 150	4,150± 710	70± 40	4,680± 620	0.24	14.7*
Nigeria	13	1,700± 400	4,290± 570	100± 30	6,950± 1,150	0.40	24.9*
United States	24	2,120± 172	4,110± 279	360± 54	5,580± 502	0.55	12.6
India	16	2,120± 310	3,290± 330	200± 40	3,540± 200	0.76	15.3*
Switzerland	9	2,260± 480	4,330± 840	190± 30	5,660± 780	0.59	12.0
Formosa	9	4,150± 1,160	19,400± 4,270	710± 170	18,600± 3,000	0.27	7.0
Thailand	10	4,910± 1,470	8,190± 1,360	470± 240	7,990± 1,980	0.64	13.7
Hong Kong	10	5,620± 950	5,470± 400	670± 150	5,900± 570	0.99	9.0
Japan	17	6,030± 800	6,200± 670	540± 90	7,640± 1,450	0.94	15.1

The metal concentrations are means, expressed as γ per gram of ash ± one standard error of the mean. The tabulated ratios are the averages of the individual ratios.

*Five patients from Ruanda-Urundi, 3 from Nigeria, and 2 from India had no measurable hepatic cadmium; hence they were omitted from the calculation of renal to hepatic cadmium ratios.

For the five groups of Negroid and Caucasoid subjects, the concentrations of renal zinc were relatively constant in comparison with the corresponding cadmium concentrations. This constancy was manifested by median concentrations which varied only from 3,100 to 4,200 γ per gram of ash, and by a total range of concentrations which varied only from 1,600 to 9,000 γ per gram of ash. On the other hand the Mongoloid subjects tended to have larger and more variable concentrations of renal zinc (Fig. 1). The highest mean concentration of zinc was the approximately 19,000 γ per gram of ash found in the Formosan kidneys and livers. The highest mean concentration of cadmium was the more than 6,000 γ per gram of ash found in the Japanese kidneys, with three of 17 samples having twice that amount. For the subjects from Hong Kong and Japan, the ratio of renal cadmium to renal zinc averaged 0.96; half of them had ratios greater than unity, but only one had twice as much cadmium as zinc.

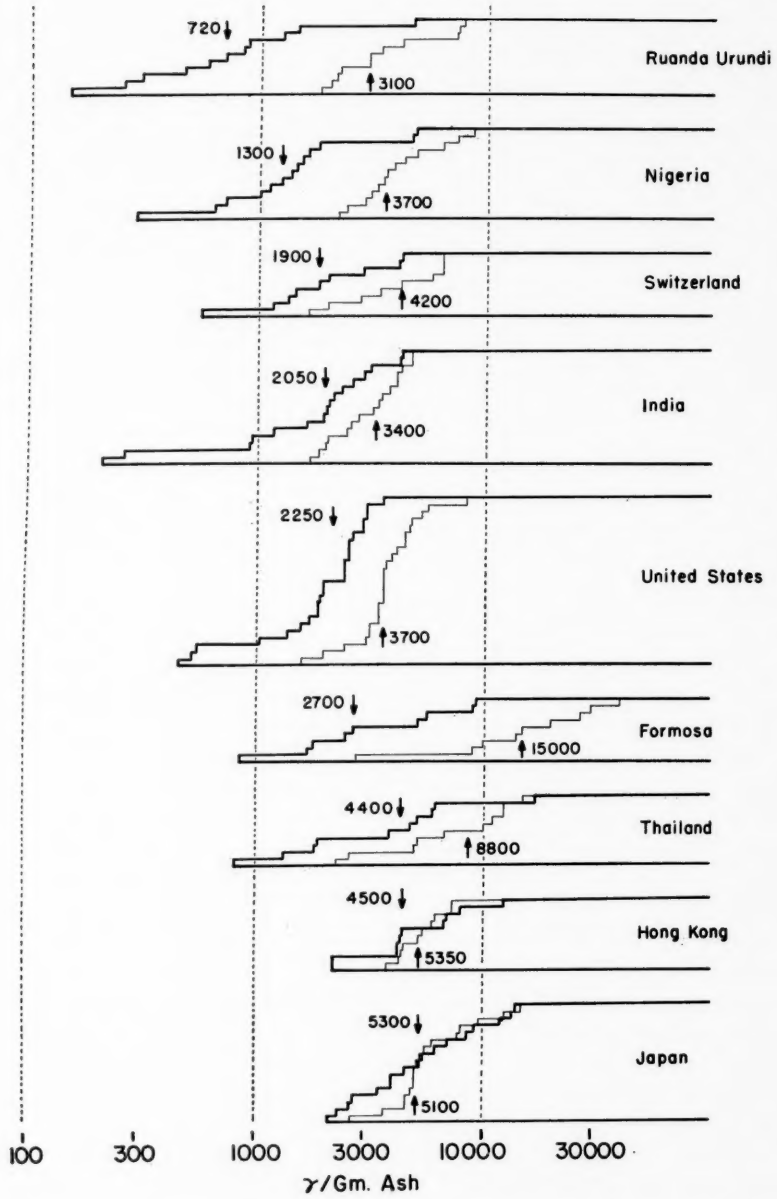

Fig. 1.—Cumulative frequency graphs of the renal concentrations of cadmium and zinc for each of the nine national groups comprising 119 adult subjects (formalin-preserved tissues). The distribution of the individual concentrations is shown for cadmium by heavy lines and for zinc by fine lines. Figures cite and arrows point to median values. The vertical scale indicates the number of patients. For instance, in the top graph each of the 11 subjects from Ruanda-Urundi is represented by one of the steps. The horizontal scale is logarithmic.

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STATISTICAL ANALYSIS

The comparison of the American children and American adults with respect to renal cadmium concentration needs no statistical analysis to demonstrate its significance. Not only is there no overlap between the youngest children and the adults, but the gap which separates them is great. On the other hand, the comparison of the renal cadmium concentrations of the nine national groups of adults has been analyzed statistically in an attempt to indicate which of the observed differences are likely to be significant.

The 119 adult subjects were divided into nine national groups. The distributions of their renal cadmium concentrations were found to be skewed. Transformation of the actual concentrations to their logarithms reduced the skewness and produced homogeneous variances for each of the nine groups (Bartlett's chi-square test: $\chi^2 = 8.59$, DF = 8, $P > 0.25$). Analysis of variance of the logarithms revealed highly significant differences among the means of the nine groups ($P < 0.001$).

Below, the means of the logarithms of the individual renal cadmium concentrations are ranked in order for each of the nine groups:

RUANDA-URUNDI	NIGERIA	INDIA	UNITED STATES	SWITZERLAND	THAILAND	FORMOSA	HONG KONG	JAPAN
2.84	3.14	3.21	3.27	3.28	3.54	3.66	3.69	3.72

The multiple comparison procedure described by Kramer[3] indicates that any two means which are underscored by the same line are not different at the 1 per cent level of significance. Similarly any two means which are not underscored by the same line are significantly different at that level. At least three different populations seem to be present. Subjects from Ruanda-Urundi differ from each of the other eight groups of subjects. In contrast the groups from Nigeria, India, the United States, and Switzerland apparently do not differ among themselves. Similarly the four groups of Mongoloid subjects do not seem to differ among themselves. As indicated in the diagram above, at the 1 per cent level of significance there is some overlap between the second and third populations, possibly due to the small sample sizes. At the 5 per cent level of significance, however, there is a distinct difference between the Caucasoid and the Negroid subjects on the one hand and the Mongoloid subjects on the other.

An attempt was also made to determine whether the nine national groups differed significantly with respect to renal zinc. The distributions of zinc concentrations within these groups were highly skewed, particularly among the Formosans. The use of logarithms reduced the skewness but did not completely

remove the significant heterogeneity of the variances. When the Formosans, who had a much higher mean zinc concentration than the other groups as well as the largest variance, were excluded, the variances of the remaining groups were homogeneous ($P > 0.05$ by Bartlett's chi-square test). Analysis of variance based on the eight remaining groups revealed highly significant differences among the means ($P < 0.001$). The means for the Formosans and the Thai, who had the highest zinc concentrations of the remaining eight groups, differed significantly ($P < 0.01$) when considered alone. It was therefore presumed that the Formosans differed significantly from all other groups.

Multiple comparisons among the remaining eight groups were performed as before with the results presented below:

INDIA	RUANDA-URUNDI	SWITZERLAND	UNITED STATES	NIGERIA	HONG KONG	JAPAN	THAILAND
3.49	3.56	3.59	3.59	3.62	3.73	3.77	3.84

The lines underscore any means which do not differ at the 1 per cent level of significance. At least two populations are indicated. One includes the Caucasoid and Negroid subjects and the other includes the Mongoloid. The Formosans, of course, comprise a third population.

COMMENT

There are few published data on renal and hepatic cadmium and zinc with which to compare our results. The mean concentrations reported here for the 24 American adults with various diseases approximate the highest concentrations observed by Koch, Smith, Shimp, and Conner,[4] who found considerable variation in 8 normal American subjects. Our data are similar to those reported for 3 normal British subjects by Smith and co-workers,[5] and for many sick American subjects by Butt and associates[6]; however, comparisons are difficult because of differences in the manner of reporting. Finally, there is no evident conflict with the semiquantitative results of Stitch.[7]

The greatest difficulty in interpreting the data just presented stems from the possible effects which various illnesses might have on tissue metals. Our preliminary investigation, like that of Tietz and his collaborators,[8] has so far failed to reveal abnormal amounts of cadmium or zinc in the kidneys or livers of patients with infections, neoplasia, cardiovascular diseases, or the miscellaneous causes of death involved here. On the other hand, decreased hepatic zinc has been described in cirrhosis of the liver,[9] and further differences in the tissue content of metals are likely to be discovered in specific pathologic conditions.

Since renal cadmium is a function of age among adults, with the maximum concentration occurring during the fifth decade,[10] the difference in age between

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American and foreign subjects might have some significance. Very small amounts of cadmium have been reported in infants[11]; our failure to find it may merely reflect the insensitivity of the spectrographic method. The high concentration of hepatic zinc which was reported here for newborn infants is in agreement with prior observations.[12]

The chemical similarity between cadmium and zinc and the reported biologic competition between them[13,14] suggested that cadmium-to-zinc ratios might be significant. Low ratios of renal to hepatic cadmium in experimental animals after cadmium administration,[15-17] even in small doses over long periods,[18] prompted tabulation of the relatively high human ratios.

SUMMARY AND CONCLUSIONS

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Renal cadmium apparently accumulated during childhood. Whereas the kidneys of American infants had no demonstrable cadmium, the kidneys of American adults always contained more than ten times the minimum measurable concentration. The concentration of renal zinc varied less with age.

The concentration of renal cadmium depended on an individual's geographic origin. One group of African adults averaged about a third as much renal cadmium as their American counterparts, the difference being statistically significant; yet the two groups were similar with respect to renal zinc. Whereas individual Caucasoid and Negroid subjects had a more than thirty fold variation in their concentrations of renal cadmium, the invariant presence of considerable amounts of renal zinc limited them to less than a sixfold variation in the concentrations of that metal. Mongoloid subjects from several different areas had considerably higher levels of both renal cadmium and zinc than did their American counterparts, with the Japanese averaging more than twice as much renal cadmium and the Formosans more than four times as much renal zinc.

Drs. Perry and Schroeder were responsible for collecting the tissues. We should like to acknowledge with gratitude the help of the following physicians who actually collected the foreign samples: Francois C. Reubi of Bern, Switzerland; Andre Piraux of Usumbura, Ruanda-Urundi; S. G. Cowper of Lagos, Nigeria; V. R. Khanolkar of Bombay and G. S. Mitel of New Delhi, India; Nong Ting of Taipei, Formosa; Pradit Tansurat of Bangkok, Thailand; Hou Pao-Chang and C. C. Lin of Hong Kong; Tetsuro Yokoyama and K. Sugai of Tokyo and Hisato Yoshimura and M. Araki of Kyoto, Japan. The collection of tissues from Africa was made possible by a grant-in-aid from the National Heart Institute of the United States Public Health Service (H-2577). The collection of tissues from Europe and Asia was made possible by a grant-in-aid from the Lasdon Foundation of Yonkers, New York. The ashing of the tissues was done at the Health Physics Division of the Oak Ridge National Laboratory at Oak Ridge, Tennessee, by K. K. McDaniel under the supervision of Miss Cook. The spectrographic analysis of tissue was done at the Department of Physics of the University of Tennessee at Knoxville, Tennessee, by Dr. Tipton and Mr. Steiner with the technical assistance of Johanna Foland, Johanna Rittner, and Sara Fentress. Dr. Allyn W. Kimball, formerly of the Mathematics Panel at Oak Ridge National Laboratory and now Professor of Biomathematics of the School of Medicine and Professor of Biostatistics of the School of Public Health at Johns Hopkins University, advised us as to the statistical section of the manuscript. The actual statistical analyses were performed by Barbara Bartels Hixon, Lecturer in Biostatistics, Department of Preventive Medicine and Public Health, Washington University School of Medicine. The metal-free formalin was prepared through the courtesy of Dr. Paul Austin of E. I. du Pont de Nemours & Co., Wilmington, Delaware.

Addendum.—The data presented in the table below became available after completion of the report. The methods of collection, preparation, and analysis were those described for foreign tissues. Although these data are few and their explanation and significance remain unknown, they substantiate the findings in the body of the report, namely, that African Negroids have less and Asiatic Mongoloids have more renal cadmium than American, European, or Asiatic Caucasoids. The renal cadmium concentrations of subjects from South Africa, Uganda, and Ethiopia were low and resembled those found in subjects from Ruanda-Urundi. The concentrations of subjects belonging to a primitive society in Gabon were higher and resembled those of Nigerians. Mongoloid Filipinos had much renal cadmium and resembled the Japanese.

RENAL CADMIUM CONCENTRATIONS (Medians and Ranges)

COUNTRY OF DEMISE	NO. OF PATIENTS	RENAL CADMIUM* MEDIAN	RANGE
Part I: 18 Additional African Negroids			
Union of South Africa	4	500	380–960
Uganda	4	755	380–1,300
Ethiopia	5	760	265–1,400
Gabon	5	1,850	1,200–5,300
Part II: 4 Additional Asiatic Mongoloids			
Philippines	4	6,450	2,100–14,000

*All concentrations are γ of cadmium per milligram of tissue ash.

We are indebted to Drs. T. D. Leontsinis and George Warren in Welkom, Union of South Africa; J. N. P. Davies in Kampala, Uganda; Ermino Codeleoncini in Addis Ababa, Ethiopia; Albert Schweitzer and Jan Bertram von Stolk in Lambarene, Gabon; and Augusto J. Ramos in Manila, Philippines, who collected the tissues.

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Sociology

HEALTH, SOCIAL STATUS, AND THE LIFE CYCLE

WALTER E. BOEK, PH.D.,* AND JEAN K. BOEK, PH.D.
ALBANY, N. Y.

From the Executive Division, New York State Department of Health and the New York State Youth Division.
(Received for publication Oct. 21, 1960)

SINCE a study of aging covers the process of life itself from conception to death, it is appropriate and necessary for representatives in a wide variety of disciplines to focus their special skills on this. Among those already beginning to contribute are social anthropologists. Some concepts from anthropology bearing on the human life cycle in terms of social status and health, therefore, are the subject of this paper. An over-all view of man in modern western society within the framework of the knowledge and methods of the behavioral sciences will be given. Among other things, this will include hypotheses about the stages people pass through from birth to death, along with human needs correlated with each period. Differences between individuals and social aging will also be noted, as well as some of the adjustment-development requirements of old age.

OLD AGE AS A PROBLEM

Western culture, as in the United States, is so significantly different from most others in the world, that it is difficult for the majority of Americans to visualize or to accept facts about how others live. At best, they are likely to romanticize or perhaps rationalize about life in other parts of the globe. One reason for differences between western and other societies is that, largely as a result of the Protestant ethic, the West has been able to produce an abundance of food. In contrast, much of the rest of the world suffers from insufficient food during certain seasons or during the whole year as a result of lack of organization, techniques, or resources either for producing and importing it, or for storing and preserving it from one season to the next.

One consequence of this difference in food supply is that life has different meanings. It is a little harder to let the unproductive cripple die when there is extra food than when food is scarce. Some societies in the past have disposed of their unproductive members, including their elderly. Whether or not he or she could still tend the garden plot was the deciding factor in the old Figi communities. Whether or not they could still keep up with family moves was a criterion for Eskimo and other nomadic groups.

Revised from an address at the 1958 Western New York Geriatrics Institute.
*Now Assistant Director, Institute for Advancement of Medical Communication, New York City.

Within the United States the age-sex pyramid is tremendously different from that in less industrialized countries in that it has a much higher ratio of old people to young. Since 1940, the total of persons 65 and over has increased by more than 60 per cent, so that the 15 million now this old constitute 9 per cent of the population.[1] By 1970, in many areas, such as New York State, this figure may go up to 11 per cent.

The basic tenet of Western society which produced the by-product of older people was essentially a dynamic, vigorous, and youthful approach to solving societal problems which precluded giving much attention to the existence or possible function of older citizens. However, the sheer force of their numbers and the complex problems of living in this society as an older citizen have made it difficult, in a democracy, to dismiss their needs as unimportant. As a result, many programs and studies are under way to understand and to meet their needs.

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Today many anthropologists, sociologists, and social psychologists apply their knowledge and skills to everyday problems confronting their own society, including those in the field of aging. This is being done at the invitation of physicians, educators, social workers, public health personnel, physical therapists, and the many other problem- and program-oriented people.

The question of how anthropologists look at human behavior scientifically may be answered by saying that, if they are trying to describe what is happening, they do not look at just a simple event. Instead they become concerned with how an act of behavior is related to other events or activities. Whenever something occurs, there is a reason, whether it is another event that has also just happened or one that occurred some time ago. Through their work within western as well as nonwestern societies, anthropologists have shown that a seemingly unimportant activity can affect many other facets of life. An example of this was the supplying of steel axes to Brazilian aborigines. Prior to this, stone axes, laboriously made by hand, were symbols of prestige merited only by tribal leaders. With the easy availability of the superior steel axes, everyone in the tribe, including young inexperienced hunters and even women, could have them. Giving this symbol to anyone, instead of only to those who through their accomplishments and their wisdom had earned it, produced a severe disruption of the whole social system. This was particularly difficult for older men whose position in society was destroyed.

Along with examination of events, the anthropologist's search for basic causes of behavior leads him to consider relationships with other people, since these are important in making the person what he is. Such contacts begin with parents, brothers, and sisters from birth and continue throughout life with all the people he meets. Humans thus cannot be scientifically regarded as isolated entities whether an analysis starts with the past, the present, or is projected into the future.

SOCIAL STATUS AS A HUMAN NEED

As a means of investigating what it means to grow old in the United States, a characteristic of human existence—the social status of individuals—will be

discussed in the next sections as it changes with the age of people. With human needs varied and numerous, one's general status and what it means in whatever group one is part of seem to be basic to many of the other needs. With social status defined as the position individuals have in relation to others, the recognition they receive, and their place in the sun, this status indicates who their friends are, who respects them, what they do for a living, and what access they have to the things they need in life.

SOCIAL STATUS IN THE LIFE CYCLE

I. Primary Helplessness.—As a basis of understanding many human problems that develop, changes in a person's social status can now be observed from birth to old age before human needs relative to these changes are discussed. When a baby is born, he is quite helpless. If it were not for the belief that it is good to have babies and to keep them alive, the neonatal would not fare very well. Love and care of children cannot just be taken for granted, however, since all societies do not value them to the same extent. An example is the treatment given to infants by the Marquesans. It started when the French attempted to change the sexually relaxed and apparently happy Marquesan family life. As a protest against this domination, the Marquesans began to de-emphasize the importance of childbearing and child care. So few infants and children were born and able to survive that as a result the whole society perished.

This helplessness of infants can be postulated as the first stage of life. The graph in Fig. 1 was prepared to show the relationship between this and other hypothesized stages through which people pass in Western society as they are born, grow up, take their places, and then leave. During the first few years of life (characterized by the label "helplessness") infants and young children particularly need older people. Surrounded by friendly elders, they are in the situation providing the intimate interaction which enhances learning—the socialization by which culture is given to the new generation.

II. Primary Dependency.—It is suggested that the average male (shown on the graph by the solid line) and female (the dashed line) start out as newborn infants in the stage of helplessness, and then enter the next stage of dependency by age 6 or 7, with girls, on the whole, achieving this slightly earlier than boys.

Although in childhood and early adolescence individuals can do many things for themselves, their families and elders in the various social systems of neighborhoods, schools, and economic organizations must provide for them in many ways, as well as exercise control over many of their activities and the things they need to have. Rough edges of infancy get knocked off, smoothed down, or modified as the whole personalities of the children are molded to fit the pattern of their society and the particular role and status they have within it. The end of this dependency status is depicted at about age 15 for boys and somewhat younger than that for girls.

Sex differences are learned early, putting boys somewhat at a disadvantage in the kind of things they can do, especially in an urban environment. Young girls can tend younger children and help with a variety of household chores. Boys can, too, except they are not supposed to be quite as helpful in doing this

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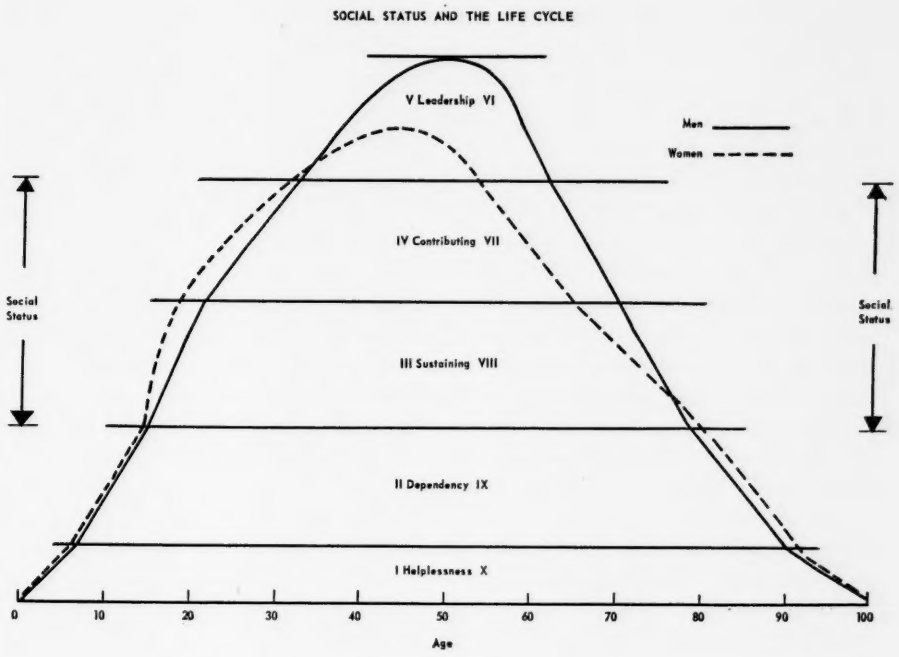

"girls'" work. Instead, boys are encouraged to go outdoors, compete in sports, and stand up for themselves.

III. Primary Sustaining Stage.—Around age 15 or so, children enter into another phase of life in which they become self-sustaining members of society. It is during these years that boys and girls have more responsibility for taking care of themselves with less guidance from their elders than they had before, and it is early in this phase that their physical growth ceases.

IV. Primary Contributing Stage.—By the time they finish their teens, many are employed and have left their parents, while quite a number have already started their own families. A fairly complete independence, at least to the point of beginning to contribute to the society more than is taken from it, starts at about age 18 for young women and about 21 for young men. In this contributing phase of life they have jobs where they produce goods and services, they have families and train their children, and they become active in social activities.

V. Primary Leadership.—The majority of people enter the highest status, that in which they serve as leaders, at about 32 years of age. Here again, women reach this stage a little earlier than men.

By describing this phase as one of leadership, we mean that people are at the height of their influence in society. During this period, men and a few women hold the top positions and wield power in most economic and professional organizations. While women take leadership roles in health, education, and welfare activities, men head civic associations. Actually both still control their offspring, for the most part. The lives of men and women differ most sharply at this stage,

for women in Western society do not achieve the level of leadership and influence which their spouses attain.

VI. Secondary Leadership.—For the typical woman, the age around 45 becomes the time when her influence begins to decline. As women go through the menopause and their children leave them, their hold on people begins to slip. This comes about because the childrearing role is not replaced by another role of equally high status in Western society. For men, leadership continues to increase until sometime around 50, but it declines after that.

VII. Secondary Contributing Stage.—At approximately 62, men as a group are back in the contributing phase. Their lives change more quickly than those of women from then on because society forces their retirement from their employment. Thus, they lose the support of the work role in maintaining their status. However, the average man keeps on contributing to some extent until he is close to 70 and a woman continues to do so until somewhere near 65. During this time men continue to work, but few advance and many have to face demotions to less responsible and less productive jobs. Women withdraw more from community affairs and have much less influence over their children and grandchildren, not being able to withstand the demands of the youth-oriented society.

VIII. Secondary Sustaining Stage.—A type of sustaining status similar to what they went through in their teens is entered by women in their middle sixties and men in their late sixties, lasting until about age 80 for women and age 78 for men. People are able to take care of themselves fairly well during these years, as a rule. Many live independently and some keep on working at part-time or seasonal jobs. Pensions, social security, savings, and other retirement plans help them to be somewhat financially secure.

IX. Secondary Dependency.—Dependency comes again around 80. At this time physiologic, sociologic and economic resources begin to be reduced to a level less than sufficient for social and economic security. The average person no longer maintains his own dwelling unit and, if he does, other younger people (such as family members, friends, or medical and nursing professionals) give essential assistance. Many live in institutions.

X. Secondary Helplessness.—After age 90, something less than a dependency status may be in store in the form of full institutional existence, although this may not be quite the same for many people as Shakespeare's "Sans teeth, sans eyes, sans taste, sans everything."

Influence of Health on the Cycle.—Charting the human life cycle for a society in this fashion should make the variables in aging stand out a little more clearly. One of the most significant of these variables, of course, is the level of health of the people, for disease or injury can quickly transform a highly productive individual into a helpless or dependent person. The state of medical knowledge and practice has had a tremendous influence on the social status of the average person as depicted by the curves in Fig. 1. As further improvements in medicine and other changes in society take place, it may be expected that the beginning of man's decline will be delayed so that there will be a broad plateau at the top of the chart and the rate of decline will be reduced, flattening out the lines which

describe his older years. Thus Fig. 1, postulated as the present situation, would need to be redrawn periodically.

Needs Common to Youth and Age.—An interest in geriatrics evolves from the problems people have when they are on the right side of the chart in the later decades of the life cycle. But aging does not begin there. It beings at the left (or even earlier, in the womb) and then follows the curves that were drawn through the stages of life that were discussed.

When attention is given to the needs of elders, it is sometimes forgotten that most of these are also requirements of younger people. Only a few are unique. The over-all desire for social status, upon which attention has been focused in this article, is implied in most of Havighurst's more specific needs listed here:

1. Personal security. People need to feel that others love, or at least, *like* them, and they need to have things turn out in a favorable or tolerable way for them. They cannot continually expect disappointments.

2. Social recognition. Individuals need to have respect from those who count in their lives.

3. A sense of self-respect. People need to be able to live up to their ideals.

4. Adequate food, clothing, shelter, and health.[2a,2b]

HUMAN NEEDS AND THE LIFE CYCLE

Variations in each of these needs as persons pass through the phases of the life cycle will now be noted.

Personal Security.—Since emotional security is achieved through intimate relationships developed with others, the child learns to respond to adults and older children in such a way that he will be rewarded with attention and care. This social interaction remains tremendously important all through life in helping the individual to remain human. Relationships he develops with others become security giving, for it is through them that he gets the re-enforcement he needs.

Once the child has passed his teens and entered the productive, contributing phase of life, his emotional security begins to come more from workmates, friends, his spouse or potential spouse, and less from parents, brothers, and sisters. Frequently there are breakdowns in such relationships, or failures to develop satisfactory ones. When this occurs, individuals frequently deviate from the main stream of society. For example, when some young people leave home to seek jobs in strange cities, they leave behind their friends and families. When work is hard to find and new friendships difficult to develop, these disappointments have to be handled alone. For some this is too difficult, causing them to follow socially unacceptable patterns of behavior.

Somewhere around age 40, most people begin to experience the loss through illness and death of people they have known and with whom they have had security-giving relationships. Attention and dependency of children also decrease as grandchildren are born and sons and daughters pursue their own lives in places that may be far away.

Not only do women have to face the loss of husbands more often than men

the loss of wives, but it is also correspondingly more difficult for women to obtain a new husband than it is for men to remarry, both because fewer men are left and because according to Western values men should marry younger women. Records show that in two-thirds of all marriages broken by death, the wife is the survivor. Three out of four women who are widowed by age 50 and 9 out of 10 who lose their husbands by age 40 live for 20 years more. Even at 65, half of the widows can expect to live 15 years, and one third are likely to live 20 years.[3] This is a long time to be without the closest companion one can ever have. By 1970 in the United States women 65 and over are expected to exceed men by nearly three million.

During these middle years, some men depend on the organizations they have built or to which they have devoted their working years to meet their security needs. Their positions demand attention or they can purchase it. However, as they reach their sixties and seventies, they become more isolated, making it still harder to achieve, maintain, or develop the needed security-giving relationships.

A fairly typical problem related to the lack of people with whom to interact occurs among older individuals. In one instance, the patient of an internist was a fairly well-off, elderly man living alone in his own home. This patient talked to imaginary people and thought his daughter-in-law was taking men into an upstairs room. Having outlived his friends, and with his children and grandchildren residing in another city, he was by himself from one day to the next. It so happened that before his physician could interest him in going out to make friends with other nearby elderly persons like himself, the patient broke his leg. This immediately brought nursing attention, his family over every day, and visits from neighbors. Almost at once he ceased reporting invisible and strange persons in his house. Unfortunately, once his leg mended and his real visitors found more important uses for their time, the imaginary people returned.

Because of the attention given to the ill, deliberate use of the sick role as a means of gaining attention and of increasing security-giving relationships is not infrequently used by oldsters, just as it is by younger adults or by children. Probably all of us can think of instances where an elderly mother or father has kept a daughter, and sometimes a son, in captivity by being a semi-invalid. If the daughter gets a beau and it looks as if she might marry, the invalid gets much worse, often in order to break up the daughter's friendship. One mother who fancied herself a singer pretended to have a heart attack to prevent her daughter from accepting a scholarship for voice training under a famous teacher. This spoiling of her daughter's big chance not only prevented her from becoming a better singer than her mother but also kept the daughter close to home. On the other hand, for most older people in our society, feigning illness cannot be relied on too long, because it will cause such a strain that they will soon be placed in an institution.

Social Recognition.—The second need listed, that of social recognition, follows the same type of course through the life cycle. One of the two main points of stress comes at the time when children are becoming adults. Because the adult role is witheld from them for a number of years, many make some attempt to get recognition in antisocial ways. The other point of stress in the life cycle has to

be faced after the middle years. The emphasis on youth in our society in conjunction with rejection of old ways brings disappointment for older people when they find that their thinking and ways of doing things are not wanted. "Let me do it, you are too slow." "You don't understand. That's not the way it's done now," are remarks that cut deeply into pride.

Self-Respect.—Closely related to recognition is the sense of worth and self-respect listed as the third need as people attempt to meet goals set for themselves. The young are full of hope and high aspirations. Life can be a happy affair as the young become physically and mentally stronger and are allowed to take greater responsibilities and to achieve their objectives in life.

But when middle and older years are reached, a person's strength is no longer increasing. Many of the ultimate goals, such as to be wealthy enough to live happily together with loving children and to have the respect of friends and colleagues, have not been achieved. During these later years, even when a job can be done well or when past experience would pay off, society will not let most people work. They are forced to retire and to experience a declining income, thus making the future even more gloomy. As they leave the bull market of their youth for the bear market of older years, it is for most more than a recession.

Many characteristics valued in Western society, such as sexual prowess, appearance, and physical and mental abilities vary greatly according to where the individuals are in the life cycle. With regard to sexual activities in particular, there is some misunderstanding and underrating of oldsters. Those concerned with problems of the elderly should profit from the realization that sexual desires and interests remain long after middle age in the typical individual.* With the genuine interests in the opposite gender not recognized by the society, the opportunities to fulfill such interests are mostly thwarted. There are a few exceptions as in retirement settlements where there are a considerable number of marriages among 60, 70, and 80-year-olds.[5] Encouragement of heterosexual interests for aged individuals actively helps reduce their dependency on younger people and on social agencies.

Food, Clothing, Shelter, and Health.—The relationship of meeting these needs to age is fairly obvious. As far as food, clothing, and shelter are concerned, the initial dependence on others is followed by the earning of money to obtain them, and then by the use of reserves or dependence on others again in older years. With reference to the life cycle graph, the keeping of old people out of the income-producing labor force is similar to exclusion of young people at the other end. It is not as much of a problem for most young people, however, because they have employed parents who pay their way.

The difficulty of remaining in the contributing or self-sustaining stages of life is exemplified when economic facts are reviewed. Forced retirement, disability, age discrimination, and other factors result in 40 per cent of the 65- to 69-year-old men not being in the labor force. This increases to 60 per cent for those 70 to 74 and 92 per cent for those 75 or over. Median annual income of families headed by people 65 or over is about half that of all families. If 65 is the

*In the small sample of older males in Kinsey, Pomeroy, and Martin's study,[4] it was not until about age 75 that one half were impotent.

retirement age, the average person will live nearly 15 years longer. Since this is over one fourth of the normal working span, it means a long time to be supported by savings or pensions.

Health is fairly directly related to age, with a build-up of strength and resistance followed by a decline as life stresses leave their mark on physiology. Dietary requirements vary somewhat as the person moves through the phases of the life cycle from birth to death. Beginning with fluids and puréed baby food, people may go through the middle phases of the life cycle with solid foods only to end up with liquids and baby food. Extra catalysts or supplements, such as vitamin capsules, iron solutions, and the like, may be required to insure the safe beginning as well as the prolongation of the essentially chemical processes of life.

Individual and Social Aging.—In a consideration of the difficulties of older people in a society, it is clear there are two kinds of aging: individual and social.[6] Individual aging involves the physiologic process of growth, skeletal changes, and circulation impairments. As a person goes past middle age, he finds that his body is systematically insulting him.[2,3] Shortened wind, greater fatigue,[7] chronic aches, and cosmetic changes betray him to society as an aging person no longer allowed to participate as actively as before in the main stream of employment or community affairs or to operate an independent household. Cosmetic or facial changes can be particularly difficult for a person to adjust to, since it is largely by this that his role is judged and wherein much of his social capital lies.

It follows then, that social aging is determined by society's definition of how individuals should be rated on the age scale of gray hair, baldness, wrinkles, forgetfulness, retirement—even if an individual exhibiting these traits does not feel he is any more ancient than those 20 years his junior. Women in their sixties and seventies still talk about going out with the other "girls" who turn out to be their same age. One fairly elderly grandmother in a hat shop was heard refusing several hats on the grounds they looked too old for her. While an old-age status may be assigned by the rest of the people, oldsters may not necessarily accept that image as belonging to themselves.

OLD AGE: THE PERIOD OF ADJUSTMENT AND DEVELOPMENT

As the individual passes the middle years, it becomes evident to him that the crises of his younger years are minor when compared to the physiologic and sociologic problems that begin to confront him.[8] In a society geared to upward striving, the ability to recognize and accept that one is slipping downward takes a lot of mental acrobatics. New problems and experiences, to be met with a reduced physical capacity in a discouraging social environment, make this period one in which an individual must develop habits and attitudes under circumstances of upheaval and stress. This is quite different from the hoped-for serenity near the end of life. The important fact in relation to needs, and one of concern to those working on programs for older people, is that when needs are not met during a significant length of time, there will be a social problem.

One developmental problem is that facing the widowed when they have to carry on the duties formerly performed for them by their spouses. When a woman loses her husband, she may have to learn how to run a business, get a job, or at

least manage her financial affairs, while a widower may have to learn how to cook, clean house, and keep his clothing in order.

Regardless of how one tries to remain young, there comes a time when everyone has to admit that he is not as young as he used to be. Shifts in amount of work and participation in social activities have to be made to a more suitable pace as one goes from middle age to the old-age groups. Because of this, community planning for housing and recreation has to achieve a balance between the advantage of helping people remain young by having them associate with youth and the disadvantage of putting them in positions where they have to compete for status with those still imbued with youthful vigor, especially when general attitudes favor the younger person.

In middle age, recreation takes the form of hobbies that often isolate an individual from others. Although this tends to relieve the person from the intense interaction faced in his occupation, especially those working under tension, it becomes a drawback as one grows older. In later years hobbies need to be more social to increase interaction, in order to replace other lost spheres of socializing such as with workmates, children, and friends.[9]

There seems to be a significant relationship between amount of interaction with others, participation in community affairs, and the ability to remain independent in older years. An effective way to prolong participation in later years is by exerting control over goods, services, or organizations. For example, property ownership can make it possible to manipulate others into obeying orders long after a person is feeble. Because property rights in most societies are enforced by social codes through appointed agents, it is not necessary for the owner to defend them with his own strength.[10]

Where a society is said to honor the elders, it is usually discovered that some do not have high status and that others have it only because they are able to benefit from prevailing respect toward older people. Those who have solid respect have acquired the necessary control over an extended family or an economic, social, or religious institution. Conversely, in societies such as ours, where the elderly in general do not have high status, there are found some men and women who do have it through financial security or the maintenance of strong family control.

SUMMARY

An attempt has been made, with the use of a graph showing social status as it correlates with age in the human life cycle, to consider life as a continual experience in which infancy, youth, adulthood, middle age, and old age merge smoothly into one another as integrated parts rather than separate entities.[11] Man is not new on earth, but having 10 per cent of a population reaching 65 years is a phenomenon known only in modern times and then only in a few societies. This accomplishment should now stimulate the development of methods which will delay the tendency of individuals to fall back into the stages of life where they become dependent on others. It is necessary to stress what the aged may do for themselves along with what society may do for them. The principle that people age most successfully when they have discovered or created for

themselves effective positions and roles in the very societies of which they are a part needs to be remembered.[10]

Society may look abstract, but the core is still interaction between humans. The aging problem may seem difficult and elusive, but the essentials are still human behavior, beliefs, and ways of doing things, as well as the love, trust, and respect of one person for another.

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Correspondence

Concerning the Daily Dose of Folic Acid

To the Editor:

In the recent article by Crosby[1] a reference[2] was cited in support of the statement that "these values [for the folic acid content of foods] are questionable, since it has been shown that the requirement of the assay organisms is not strictly for folic acid (pteroylglutamic acid). It was possible to use fragments of folic acid and other glutamates in place of pteroylglutamic acid. Hence the results of bioassay are high when interpreted in terms of pteroylglutamic acid." However, this reference[2] does not corroborate such a statement. Instead the article[2] pointed out that *Streptococcus faecalis* responds to pteroylglutamic acid and pteroic acid, but not to pteroyltriglutamic acid or pteroylheptaglutamic acid, and that *Lactobacillus casei* responds to pteroylglutamic acid and pteroyltriglutamic acid but not to pteroic acid or pteroylheptaglutamic acid, so that, when the two assay procedures are both used, the lower value should indicate the pteroylglutamic acid content of the sample. Subsequently an elaborate and exhaustive collaborative study by nineteen laboratories showed that there was good agreement between the *S. faecalis* and *L. casei* assays of food samples and that the microbiologic values actually tended to be lower than those obtained by animal assay.[3] There is no indication that erroneously high values are obtained by the generally used microbiologic procedures. The validity of these procedures was implicit in the studies that led to the isolation of folic acid from liver and spinach (reviewed by Jukes and Stokstad). The folic acid content of "normal" diets varies according to their composition, but numerous assays indicate that green leaves such as spinach contain about 1 to 2 mg. of folic acid per 100 Gm. of dry matter and a "good" diet could supply about 400 μg daily.

Evidently not all diets are adequate, for the occurrence of anemia due to folic acid deficiency continues to be frequently reported,[4-7] and in a current effort to obtain relapsed cases of pernicious anemia, our various collaborators have reported that a number of the patients, upon critical examination, have been found to be suffering from folic acid deficiency and do not have pernicious anemia.

The studies by Sheehy[8] cited by Crosby[1] are at present available only in abstract form. It would be of interest to learn whether antibiotics had been received by the patients in these studies. Earlier work in Puerto Rico by Suarez and Morales communicated to us led to the conclusion that 2.5 to 7.5 mg. of folic acid daily was not quite sufficient for the treatment of sprue.

The predominance of neurological lesions in a large proportion of patients with pernicious anemia is an observation recorded in various textbooks of hematology which long preceded the introduction of folic acid into medicine in 1946. The compilation by Davidson[9] indicated that cord symptoms in pernicious anemia were more prominent in the years prior to 1926 than in the period 1944 to 1956. The tacit assumption that neurological symptoms in a patient with pernicious anemia are due to the ingestion of multivitamin preparations containing folic acid[1] rests upon uncontrolled observations that permit alternate conclusions to be drawn.

Thomas H. Jukes

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Reply by Colonel Crosby

To the Editor:

Thank you for the opportunity of clarifying my reference to Dr. Jukes' paper. The purpose in citing his paper was to designate an authoritative reference to the microbic models employed in the assay of "folic acid" and their inability to discriminate between various molecules with FA activity. Dr. Jukes in his letter provides an example of this lack of discrimination, but the versatility of the assay organisms in utilizing various molecules is somewhat broader than his example would indicate.

In the letter Dr. Jukes states, "There is no indication that erroneously high values are obtained by the generally used microbiologic procedures." If he refers to the requirements of organisms employed for the microbiologic procedures, he is correct. If he is referring to the requirements of mature humans, he has misinterpreted my editorial: there is indeed some indication that the generally used microbiologic procedures do not accurately measure the FA factor required by humans.

FA of biologic origin (e.g., in spinach) has been assayed in microbiologic systems to establish a ratio of activity to weight. These biologic materials contain a variety of molecules which can satisfy the FA requirement of bacteria. When synthetic FA (almost pure pteroylglutamic acid) is subjected to the same microbiologic assay there appears to be no discrepancy. However, when biologically derived FA material is used in human deficiency states the daily dose is at least 2.5 mg., as Dr. Jukes points out. With synthetic material the daily dose is .025 mg. It is this discrepancy which suggests the need for re-examination of the microbiologic methods in terms of human requirement.

The last paragraph of Dr. Jukes' letter is misleading. In my editorial to which he refers there is no assumption, tacit or otherwise, that "neurological symptoms in a patient with pernicious anemia are due to the ingestion of multivitamin preparations containing folic acid." I know of no one who believes this to be so.

William H. Crosby

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Book Reviews

A CLINICAL PROSPECT OF THE CANCER PROBLEM. By D. W. Smithers, M.D., F.R.C.P., F.F.R. Edinburgh, 1960, E. & S. Livingstone, Ltd. Pp. 232, indexed. Price $8.50, Williams and Wilkins Company, exclusive U.S. agents.

This book serves as a general introduction to a series of volumes describing neoplastic diseases arising at several sites. In it, editor Smithers is by turns conjectural and philosophic as he comments on several widely acknowledged cancer theories and draws upon his extensive clinical experience for the element of a more embracing view.

In the early chapters, the concept of cancer as a distinct disease entity stemming from a cancer cell which has suddenly become endowed with a heritable malignant characteristic is discredited. In Smithers' view, cancer is no sudden irreversible intracellular change, but rather an ill-defined advanced stage of tissue disorganization to which most complex organisms become increasingly prone with age. It stems from those environmental conditions most prone to stimulate tissue growth and dedifferentiation to a degree of activity beyond the organism's regulative capabilities—witness tissue metaplasia, the multicentric origin of tumors, the slow progression and occasional regression of some neoplastic diseases, and the responsiveness of certain cancers to hormone administration.

In his later chapters, the author considers the currently available therapeutic modalities. He pictures operation and radiotherapy as the only methods regularly successful in dealing with neoplastic processes; the former, by removing the anatomic source of the disorder, and the second, by destroying dividing cells and permitting local tissue controls to be re-established. Successful hormonal therapy of cancer requires retention of sufficient tissue differentiation, as does the beneficial use of radioactive iodine in thyroid cancer.

Chemotherapy is pictured as still in its infancy and still too much guided by the concept of the special evils of *cancer cells* which can and must be destroyed. Further, much of current cancer research is criticized as displaying the same conceptual limitations. In place of the indiscriminate drug-testing programs, Smithers eloquently pleads for more attention in therapy to "thoughtful palliation" and more attention in research to the problems of tissue growth and development and its biologic control.

Albert H. Owens, Jr.

BIOLOGY OF PYELONEPHRITIS. Edited by Edward L. Quinn, M.D., F.A.C.P., and Edward H. Kass, M.D., Ph.D., M.A. (hon.), F.A.C.P. Boston, 1960, Little, Brown & Company. Pp. 708, indexed. Price $18.00.

This book records the proceedings at a Henry Ford Hospital International Symposium held in late 1959. It is a most unusual volume, and reflects the care and imagination of the program committee, as well as the high quality of the distinguished participants. The list of contributors is like a "Who's Who in Renal Physiology and Pyelonephritis": Beeson, Berliner, Braude, Brod, Darmady, Dent, Epstein, Finland, Gottschalk, Guze, Jackson, Kass, Kark, Kimmelstiel, Kunin, Mudge, Oliver, Page, Pitts, Raaschou, Relman, Shapiro, Strauss, Welt, and Wirz are only a few of the names. The topics range from histochemistry to genetics, microbiology to urologic instrumentation. Here, in one place, are most of the relevant data and orienting attitudes on pyelonephritis. A superb compilation for anyone interested in this disease.

Louis Lasagna

INFECTIOUS DISEASES OF CHILDREN. Second edition. By Saul Krugman, M.D., and Robert Ward, M.D., St. Louis, 1960, The C. V. Mosby Company. Pp. 398, indexed. Price $13.00.

Since the publication of the first edition in 1958, this text has already become something of a classic in the literature of pediatrics and infectious disease. The great advances of the last few years, particularly in the area of virology, have made the publication of the second edition a reasonable step.

The new portions in the second edition have continued the pattern of excellence found in the first. Especially valuable is the new chapter entitled "Acute Respiratory Infections." This section summarizes and clarifies the abundant literature on the respiratory syndromes produced by the newer agents, such as the parainfluenza viruses, the respiratory syncytial virus, the Eaton-Liu virus, and certain of the ECHO viruses. Much of the recent information concerning the ECHO viruses has also been assimilated in a new chapter on the enteroviruses, which replaces separate chapters on poliomyelitis and the Coxsackie viruses in the previous edition.

Other significant additions include a new chapter on rabies. This disease, although rare, presents a problem of some magnitude in regard to prophylaxis, since rabies vaccine is administered to about 50,000 patients each year in the United States. Sections on the antimicrobial treatment of acute bacterial meningitis and staphylococcal infection have been revised to conform with recent developments. Diphtheria immunization of adolescents and adults has been discussed in more detail.

The authors do not intend this to be an all-inclusive textbook on infectious disease and have chosen not to include the leptospiral, mycobacterial, and mycotic diseases. Cytomegalic inclusion body disease and *Pneumocystis carinii* infection are also omitted, despite recent pediatric interest in these entities. This book, however, was intended to fill the need for a concise guide to the common infections of childhood. The authors, in this edition as in the last, have succeeded in doing this in admirable fashion.

Edward J. Ottenheimer, Jr.

THE NEW YEAR BOOK OF DRUG THERAPY, 1960-61 Series. Edited by Harry Beckman, M.D. Chicago, 1961, The Year Book Publishers, Inc. Pp. 587, indexed. Price $8.50.

A cover-to-cover reading of this latest *Year Book of Drug Therapy* is disquieting. The editor's task of canvassing the year's therapeutic claims is, admittedly, a difficult one. Perhaps one could not demand the inclusion only of those studies apparently performed with finesse and sophistication by reputable investigators and published in first-class journals. But can one defend the inclusion of poorly devised and poorly described therapeutic misadventures? Dr. Beckman slams away at some of these latter papers in his editorial addenda, but other equally bad papers he seems to swallow whole. In addition, the articles in some sections (notably the neuropsychiatric medley) are arranged in no rational order and give one the impression of a hasty pudding.

One of the problems is the necessity for the editor to be an expert in all therapeutic fields. Dr. Beckman might be wise to use special field editors, so as to avoid the errors of omission or commission that so easily accompany superficial knowledge of any field. He might also consider adding a yearly follow-up of the therapeutic claims of yesteryear, on the "advances" recorded in previous *Year Books* and shown to be nonsense by later studies.

Finally, a word about the "simplest of statistical tests" to which the editor refers on p. 117, and originally accredited by Alan Gregg to R. A. Fisher. The test's application was never clearly spelled out by Gregg in his book, and Dr. Beckman employs it irrelevantly in this *Year Book*. One is really not interested in whether the results with a treatment are significantly different from a 50-50 "success-failure" split, as implied by both Gregg and Beckman, but in either the difference between results after treatment and results after no treatment, or the difference between two treatments. Thus Fisher's "quickie test" could have been usefully applied to the abstract on pp. 218-219 but not to the abstract actually cited on p. 117.

Louis Lasagna

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CIBA FOUNDATION SYMPOSIUM ON CELLULAR ASPECTS OF IMMUNITY: edited by G. E. W. Wolstenholme and C. M. O'Connor. Boston, 1960, Little, Brown & Company. Pp. 495, indexed. Price $10.50.

In June of 1959, another in the distinguished series of Ciba Symposia was held, dealing with the problems of immunity and antibody formation considered from the currently popular aspect of the cellular basis of these phenomena. With the reappraisal of these problems which has been occurring in the past few years, fresh interest has been focused on the antibody-forming cell as the functional unit which represents the key to the complex mechanisms of the immune response. Great attention is being given to characterizing the immunologically competent cell and to interpreting knowledge of immune mechanisms from a cellular, rather than a molecular, point of view. Thus, a symposium concerned with this important area of vigorous current investigation is, indeed, a worthy and timely undertaking. This volume is a record of the proceedings of that meeting presented in the familiar form of a series of papers, interspersed with informal discussion by the participants. Many of the papers are of a review nature, and are accompanied by representative bibliographies. Some of the leading investigators in the field took part in the conference, contributing generally cogent papers and an often provocative informal exchange of ideas.

A wide range of important topics was considered. The "clonal selection theory" of antibody formation, the grand hypothesis which has been at the center of the recently reawakened speculation, received extensive discussion and evaluation. This concept of antibody production, involving a "selective" stimulation of a genetically predetermined cell, or group of cells, already possessing the capacity to produce antibody complementary to the antigen, was the unifying theme of the entire conference. Repeatedly, it was made evident that, while currently appearing to provide the most inclusive explanation of many immune phenomena, the selection hypothesis still awaits conclusive experimental confirmation. In addition, many of the basic questions about the immune response which remain unanswered were under consideration. Prominent among these, the critical phenomenon of immune tolerance and recognition of self was reviewed, with current theories and evidence summarized in the light of the cellular theory. The important question of how immunologic information is lodged in the cell, and how it is transmitted over long periods of time ("immunologic memory") was considered. As a sequel to this problem, the intriguing evidence on the transfer of delayed hypersensitivity in man was described, raising the question of whether this immunologic information can be passed on to other cells by any process other than genetic descent. Recent advances in characterizing the immunologically competent cell through impressive microscopic studies and correlated functional observation were reported. In the discussion of these and related problems, the majority of the information and evidence presented had already been published, or was about to be published in detail elsewhere, and thus was usually well known to the participants. As a result, this was the type of symposium which attempts to summarize and bring the particular problem into focus, and hopefully, to suggest avenues for future pursuit.

It would seem that this most recent Ciba undertaking easily establishes its worthiness to the investigator and the interested clinician alike on several scores: as a source of information and reference, as a summary of the present status of knowledge in the field, and as an indicator of areas of current and future investigation. The book suffers somewhat from a tendency for some of the discussion to wander, and from the passage of a fair amount of time (in this active field) between the meeting and the publication of this volume. However, these difficulties are relatively minor and, for the most part, unavoidable. In all, this is indeed a commendable addition to an outstanding series and to the medical bookshelf.

David J. Gocke

Announcements

The NINTH ANNUAL MEETING OF THE CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION will be held on Thursday, Friday, and Saturday, Aug. 24 to 26, 1961, in the Bessborough Hotel, Saskatoon, Saskatchewan. The scientific sessions will meet on Thursday and Friday at the Auditorium of the University Hospital.

All physicians interested in Physical Medicine and Rehabilitation are welcome to attend this conference. For further information, write to Maurice Mongeau, M.D., Secretary-Treasurer, 6265 Hudson Road, Montreal 26, Quebec.

The Department of Health, Education, and Welfare has announced the availability of PLANNING OF FACILITIES FOR MENTAL HEALTH SERVICES. This report of the Surgeon General's Ad Hoc Committee on Planning for Mental Health Facilities may be purchased from the Superintendent of Documents, United States Government Printing Office, Washington 25, D. C., for 40 cents per copy. (Public Health Service Publication No. 808. Pp. 55. 40¢.)

The ARTHRITIS AND RHEUMATISM FOUNDATION offers predoctoral, postdoctoral, and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning July 1, 1962. Deadline for applications is October 31, 1961.

These awards are intended as fellowships to advance the training of young men and women of promise for an investigative or teaching career. They are not in the nature of a grant-in-aid in support of a research project.

The program provides for three awards: (1) *Predoctoral Fellowships* are limited to students who hold a bachelor's degree. Each applicant studying for an advanced degree must be acceptable to the individual under whom the work will be done. These Fellowships are tenable for one year, with prospect of renewal. Stipends range from $2,000 to $3,000 per year, depending upon the family responsibilities of the Fellow; (2) *Postdoctoral Fellowships* are limited to applicants with the degree of Doctor of Medicine, Doctor of Philosophy—or their equivalent. These Fellowships are tenable for one year, with prospect of renewal. Stipends range from $5,000 to $7,000 per year, depending upon the family responsibilities of the Fellow; and (3) *Senior Investigator Awards* are made to candidates holding or eligible for a "faculty rank" such as Instructor or Assistant Professor (or equivalent) and who are sponsored by their institution. Stipends are from $7,000 to $10,000 per year and are tenable for five years.

A sum of $500 will be paid to cover the laboratory expenses of each Postdoctoral Fellow. An equal sum will be paid to either cover the tuition expenses or laboratory expenses of each Predoctoral Fellow. In the case of Senior Investigators, instead of the $500, an additional 10% of the stipend will go to the institution to be applied to annuity programs, laboratory expenses, travel, etc.

For further information and application forms, address the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N. Y.

ERRATUM

Figs. 1 and 7 of the article, "Problems of Rehabilitation of the Leprosy Patient in a High Prevalence Area of Africa," by M. F. Lechat, M.D., and F. Puissant, M.D., (J. CHRON. DIS. 13:221, 1960) are original illustrations. These were credited in this publication as reproductions from Editions Arscia S.A., Bruxelles.